

Effects of Coenzyme Q₁₀ in Early Parkinson Disease

Evidence of Slowing of the Functional Decline

Clifford W. Shults, MD; David Oakes, PhD; Karl Kieburtz, MD; M. Flint Beal, MD; Richard Haas, MB Chir; Sandy Plumb, BS; Jorge L. Juncos, MD; John Nutt, MD; Ira Shoulson, MD; Julie Carter, RN, MS, ANP; Katie Kompoliti, MD; Joel S. Perlmutter, MD; Stephen Reich, MD; Matthew Stern, MD; Ray L. Watts, MD; Roger Kurlan, MD; Eric Molho, MD; Madaline Harrison, MD; Mark Lew, MD; and the Parkinson Study Group

Background: Parkinson disease (PD) is a degenerative neurological disorder for which no treatment has been shown to slow the progression.

Objective: To determine whether a range of dosages of coenzyme Q₁₀ is safe and well tolerated and could slow the functional decline in PD.

Design: Multicenter, randomized, parallel-group, placebo-controlled, double-blind, dosage-ranging trial.

Setting: Academic movement disorders clinics.

Patients: Eighty subjects with early PD who did not require treatment for their disability.

Interventions: Random assignment to placebo or coenzyme Q₁₀ at dosages of 300, 600, or 1200 mg/d.

Main Outcome Measure: The subjects underwent evaluation with the Unified Parkinson Disease Rating Scale (UPDRS) at the screening, baseline, and 1-, 4-, 8-, 12-, and 16-month visits. They were followed up for 16 months or until disability requiring treatment with levodopa had developed. The primary response variable was the change

in the total score on the UPDRS from baseline to the last visit.

Results: The adjusted mean total UPDRS changes were +11.99 for the placebo group, +8.81 for the 300-mg/d group, +10.82 for the 600-mg/d group, and +6.69 for the 1200-mg/d group. The *P* value for the primary analysis, a test for a linear trend between the dosage and the mean change in the total UPDRS score, was .09, which met our prespecified criteria for a positive trend for the trial. A prespecified, secondary analysis was the comparison of each treatment group with the placebo group, and the difference between the 1200-mg/d and placebo groups was significant (*P* = .04).

Conclusions: Coenzyme Q₁₀ was safe and well tolerated at dosages of up to 1200 mg/d. Less disability developed in subjects assigned to coenzyme Q₁₀ than in those assigned to placebo, and the benefit was greatest in subjects receiving the highest dosage. Coenzyme Q₁₀ appears to slow the progressive deterioration of function in PD, but these results need to be confirmed in a larger study.

Arch Neurol. 2002;59:1541-1550

PARKINSON DISEASE (PD) is a degenerative neurological disorder that is characterized by resting tremor, slowness of movement, and muscular rigidity. Parkinson disease affects approximately 1% of Americans older than 65 years.¹ The cardinal pathological features of PD are loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies in neurons in the substantia nigra and extranigral regions of the brain.^{2,3}

The causes of PD are not fully understood,⁴ but genetic abnormalities and environmental factors have been associated with PD.^{5,6} Recognition that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can cause parkinsonism through the inhibition of complex I in the mito-

chondrial electron transport chain stimulated studies of mitochondrial function in PD.^{7,8} Schapira et al⁹ and Turner and Schapira¹⁰ reported a selective decrease in

For editorial comment see page 1523

complex I activity in the postmortem substantia nigra in patients with PD. Parker et al¹¹ first reported and others confirmed¹²⁻¹⁴ a decrease in complex I activity in platelets from patients with PD.

The likelihood that a reduction in complex I activity plays a role in the pathogenesis of PD was strengthened by the demonstration that patients with early, untreated PD have reduced activity of complex I and II/III in mitochondria isolated from platelets and that treatment with le-

Author affiliations are listed at the end of the article.

vodopa and selegiline hydrochloride does not affect mitochondrial function.^{15,16} The possibility that a systemic insult to the mitochondria could preferentially injure nigral dopaminergic neurons has been supported by the demonstration that systemic administration of rotenone, which inhibits complex I but is not selectively taken up into dopaminergic neurons, causes preferential injury to the nigral dopaminergic neurons in rats.¹⁷

Coenzyme Q₁₀ is the electron acceptor for complexes I and II and also a potent antioxidant. Shults et al¹⁸ demonstrated reduced levels of coenzyme Q₁₀ in the mitochondria isolated from platelets of patients with PD, and the serum level of coenzyme Q₁₀ in patients with parkinsonism has been reported to be significantly lower than that in age-comparable patients with stroke.¹⁹ Beal et al²⁰ demonstrated that oral supplementation with coenzyme Q₁₀ reduced the loss of dopamine and dopaminergic axons in the striatum in 1-year-old mice treated with MPTP. Matthews et al²¹ found that oral supplementation with coenzyme Q₁₀ in rats resulted in significant increases in the concentration of coenzyme Q₁₀ in mitochondria in the cerebral cortex. In a pilot study, Shults et al²² demonstrated that oral consumption of coenzyme Q₁₀ at dosages of 400, 600, or 800 mg/d by patients with PD was well tolerated and resulted in significant elevations of plasma levels of coenzyme Q₁₀. On the basis of this work, we undertook a dosageranging study to evaluate the safety and tolerability of high dosages of coenzyme Q₁₀ in patients with early PD and the ability of coenzyme Q₁₀ to reduce the rate of functional decline in such patients.

METHODS

ORGANIZATION

This multicenter study was organized by the University of California–San Diego in conjunction with the Parkinson Study Group; the Clinical Trials Coordination Center and the Department of Biostatistics at the University of Rochester, Rochester, NY; the Department of Neurology and Neuroscience at the Weill Medical College of Cornell University, New York, NY; and the enrolling sites. The National Institute of Neurological Disorders and Stroke sponsored the trial. Coenzyme Q₁₀ and matching placebo were supplied by Vitaline Corp, Ashland, Ore. Ten investigators at 10 Parkinson Study Group sites in the United States were responsible for the recruitment, enrollment, and follow-up of subjects. The institutional review board at each site reviewed and approved the protocol. The principal investigator and the Steering Committee guided the trial. The Safety Monitoring Committee, established by the Steering Committee, and the Performance and Safety Monitoring Board, constituted by the National Institute of Neurological Disorders and Stroke, independently and periodically reviewed enrollment, premature terminations, end points, adverse events, and laboratory results.

RECRUITMENT, ENROLLMENT, AND RANDOMIZATION

Eighty subjects with early PD were enrolled in the study at 10 sites. Inclusion criteria required the presence of all 3 cardinal features of PD (resting tremor, bradykinesia, and rigidity), which had to be asymmetrical. The diagnosis of PD must have been made within the previous 5 years in men or in women 30 years or older. Women must have been postmenopausal for at least

2 years or surgically sterile or using a reliable form of contraception for at least 2 months before screening and must have agreed to continue its use for the duration of participation in the study.

Exclusion criteria included the following:

1. The use of any medication for PD for 60 days before the baseline visit.
2. Parkinsonism due to drugs.
3. The use of antioxidants such as selegiline, vitamin E, and ascorbic acid (vitamin C) within 60 days of the baseline visit, and previous use of coenzyme Q₁₀ within 120 days of the baseline visit. There was no limitation on the use of antioxidants before pretrial discontinuation of therapy. Patients were asked to take a standard daily multivitamin without minerals but no other supplemental vitamins.
4. The use of drugs known to interfere with mitochondrial activity.
5. The use of methylphenidate hydrochloride, cinnarizine, reserpine, amphetamines, or monoamine oxidase-A inhibitors within 6 months before the baseline visit.
6. An unstable dosage of drugs active in the central nervous system (eg, anxiolytics, hypnotics, benzodiazepines, and antidepressants) during the 60 days before the baseline visit.
7. The use of appetite suppressants within 60 days before the baseline visit.
8. Diseases with features of PD (eg, progressive supranuclear palsy, essential tremor, multiple system atrophy, striatonigral degeneration, olivopontocerebellar atrophy, and postencephalitic parkinsonism).
9. A history of active epilepsy.
10. The presence of dementia as evidenced by a Mini-Mental State Examination score of less than 24.²³
11. The presence of depression as indicated by a score on the Hamilton Depression Rating Scale of greater than 10.²⁴
12. A history of stroke.
13. Disability sufficient to require treatment with dopaminergic drugs, as determined by the enrolling investigator.
14. A modified Hoehn and Yahr Scale score of greater than 2.5.²⁵
15. The presence of other serious illnesses.
16. Participation in other drug studies or the use of other investigational drugs within 30 days before screening.
17. A history of electroconvulsive therapy.
18. A history of brain surgery for PD.
19. A history of structural brain disease.
20. A tremor score on the Unified Parkinson's Disease Rating Scale (UPDRS) of 3 or greater.²⁵

At the screening visit, after the nature, purpose, and potential risks and benefits of the study were explained to the subject, written informed consent was obtained. The subject underwent evaluation with a medical history, physical examination, and a battery of clinical assessments of PD (the UPDRS,²⁵ the Hoehn and Yahr Scale,²⁵ the Schwab and England Scale,²⁵ and a timed tapping task). Previous studies have established good interrater reliability for the UPDRS.^{26–28} For the timed tapping task, the subject alternately touched 2 counters, separated by 20 cm, with the index finger of 1 hand as many times as possible during 1 minute. Subjects performed 2 trials with each hand.

Screening laboratory studies included electrocardiography, a chemistry panel (levels of albumin, alkaline phosphatase, aspartate transaminase, alanine transaminase, bicarbonate, serum urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, phosphorous, potassium, sodium, total bilirubin, total creatine kinase, total protein, and uric acid), complete blood cell count, and urinalysis.

The baseline visit occurred within 1 month of the screening visit. In addition to the clinical assessments of PD, a blood

sample (approximately 110 mL) was obtained to determine complex I activity in platelets and levels of coenzyme Q₁₀ in plasma.²² On completion of the baseline visit, each patient was randomly assigned to receive coenzyme Q₁₀ at a dosage of 300, 600, or 1200 mg/d or matching placebo in a 1:1:1:1 allocation using a computer-generated randomization plan that included stratification by the investigator and blocking (with a block size of 8) to ensure that each investigator had approximately the same number of subjects assigned to each treatment group. Subjects, enrolling investigators, enrolling coordinators, and other personnel involved in the care of the patients and the acquisition and analysis of data were masked to treatment assignment until completion of the study.

Participants underwent reevaluation at 1, 4, 8, 12, and 16 months (± 7 days) after the baseline visit using the battery of clinical examinations, and the enrolling investigator determined whether sufficient disability had developed to require treatment with levodopa. Each subject was followed up for 16 months or until the investigator determined that the patient needed treatment with levodopa. A blood sample was again drawn at the final visit for evaluation of platelet mitochondrial function and plasma levels of coenzyme Q₁₀. Safety laboratory studies (chemistry panel, complete blood cell count, and urinalysis) were performed at the 1-, 4-, and 8-month and final visits.

INTERVENTION

Each patient was randomly assigned to receive coenzyme Q₁₀ at a dosage of 300, 600, or 1200 mg/d or matching placebo. The study medication was taken 4 times each day, with breakfast, lunch, and dinner and at bedtime. The wafers with active study drug contained 300 mg of coenzyme Q₁₀ and 300 IU of vitamin E as a lipophilic carrier. Matching placebo wafers also contained 300 IU of vitamin E each.

OUTCOMES, STATISTICAL METHODS, AND SAMPLE SIZE

Safety and Tolerability

All adverse events (using World Health Organization terminology) and abnormal laboratory values were analyzed by treatment group and severity. Only new events not present at the screening or the baseline visit were counted. The Cochran-Armitage exact test for trend (1-tailed) was used to compare treatment groups with regard to the proportion of subjects experiencing a particular adverse event or an abnormal laboratory value.²⁹ We used 1-tailed tests because the finding of poorer tolerability in the placebo group would have been highly unlikely and of no interest. Compliance, as measured by pill counts, was summarized descriptively by treatment group.

Efficacy and Trial Design

The primary response variable was the change in the total score on the UPDRS from the baseline to the last visit. The last visit was that at which the investigator judged that disability requiring levodopa therapy had developed, the last visit before a premature termination, or the 16-month visit. At each visit, the investigator was asked to assess whether the subject had reached disability sufficient to require therapy with levodopa using a form that asked a series of questions regarding occupation, gait, balance, finances, domestic responsibility, and activities of daily living. The series of questions was based on our previous experience with this end point.³⁰ The decision was the responsibility of the enrolling investigator. The choice of initial antiparkinsonian therapy was also the responsibility of the enrolling investigator and could include levodopa, dopaminergic ago-

nists, selegiline, amantadine hydrochloride, and anticholinergic drugs.

The primary statistical analyses were performed according to the intention-to-treat principle.³¹ According to the prespecified primary analysis plan, the mean change in the total UPDRS score was determined for each treatment group (300-, 600-, and 1200-mg/d and placebo) and tested for a linear trend between the dosage and mean change in the UPDRS using analysis of covariance. Analyses were adjusted for the baseline score and investigator. This analysis allows identification of a beneficial response when there is a clear dose-response effect and when the effects at all of the dosages tested are equivalent.³² Because this dosage-ranging study was designed to detect a trend toward efficacy, not to demonstrate efficacy *per se*, we specified use of a less stringent criterion than usual for declaring statistical significance, namely a 1-sided *P* value of .10. However, we present our efficacy data using 2-sided *P* values.

Sample Size

Based on these suppositions and our previous experience,³⁰ the study was projected to have 73% power to detect an effect of coenzyme Q₁₀ corresponding to a difference of 6 points in total UPDRS score between the placebo group and the highest active-dosage group.

We also explored other analyses. As specified, we performed analyses comparing all combined active-dosage groups against the placebo group and each active-dosage group against the placebo group using analysis of covariance. For these secondary analyses, we did not adjust for multiple comparisons. We examined the area under the curve, ie, accumulated changes in total UPDRS score during the total duration of the study, and the trajectories of these curves to assess whether the effect of coenzyme Q₁₀ on total UPDRS score was more consistent with predominantly short-term effects on symptoms or long-term effects on disease progression. Time to disability sufficient to require treatment with levodopa was analyzed using the method of Kaplan and Meier and the Cox proportional hazards regression model stratified by investigator.³³

Plasma Level of Coenzyme Q₁₀

Subjects were asked to not take study medication after the last dose on the day before follow-up visits to obtain a plasma level representative of a steady state. The samples were kept at each site at -80°C until shipped on dry ice to the laboratory at Weill Medical College of Cornell University. Assays for plasma levels of coenzyme Q₁₀ were performed by means of techniques previously described with modification.¹⁶ The values from 1 subject, who was assigned to receive coenzyme Q₁₀ at a dosage of 600 mg/d, appeared to represent a reversal of the baseline and final visits and were not included in the analysis.

Comparisons of plasma levels at the final visit among patients treated with coenzyme Q₁₀ and placebo were made using analysis of covariance, adjusting for the baseline value as a covariate.

Mitochondrial Assays

At the baseline and final visits, venous blood was collected into two 50-mL syringes containing 5 mL of anticoagulant sodium citrate solution. The samples were transferred at room temperature to the Mitochondrial Research Laboratory at the University of California-San Diego by overnight courier. Complex I and citrate synthetase activities were measured by means of well-established techniques.²² The Mitochondrial Research Laboratory, University of California-San Diego, also performed the assay for complex I/III using the rotenone-

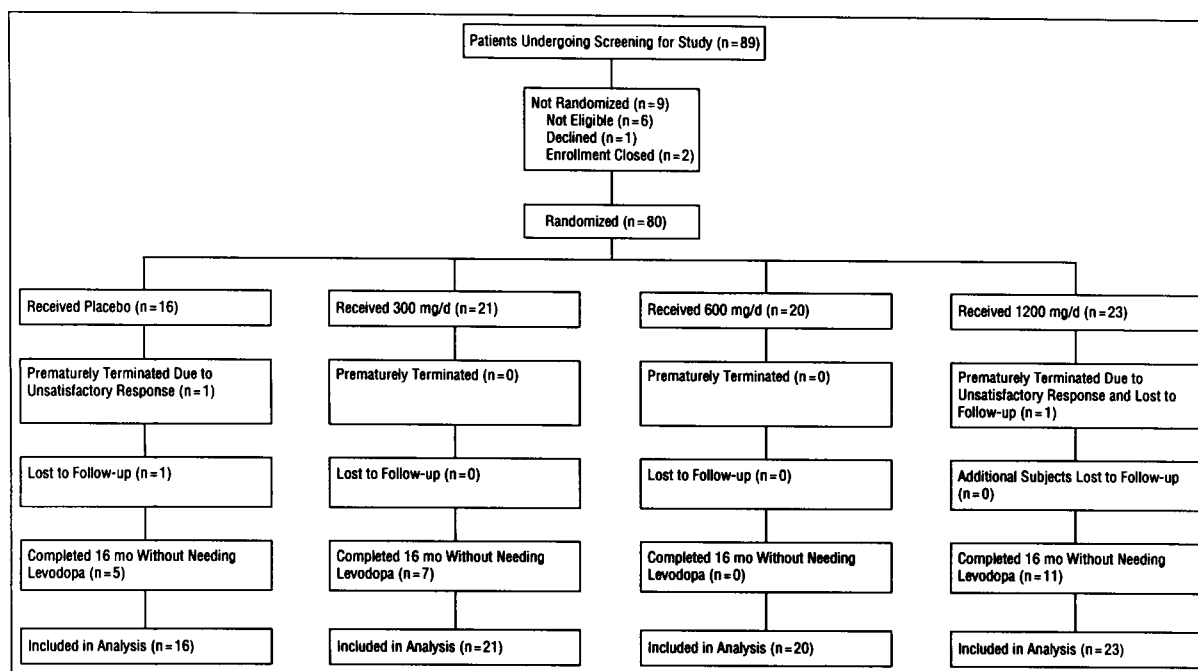


Figure 1. Patient flowchart.

Table 1. Baseline Characteristics*

	Coenzyme Q ₁₀ Groups				P Value
	Placebo Group (n = 16)	300 mg/d (n = 21)	600 mg/d (n = 20)	1200 mg/d (n = 23)	
Male, No. (%)	12 (75)	12 (57)	14 (70)	14 (61)	.64
Age, y	63.1 (12.1)	60.9 (10.8)	61.9 (11.7)	59.9 (11.2)	.84
Total UPDRS score	24.1 (6.4)	23.9 (9.8)	23.0 (11.1)	22.7 (10.7)	.96
UPDRS mental score	0.88 (1.15)	0.71 (0.72)	1.10 (1.12)	0.70 (0.97)	.53
UPDRS motor score	17.8 (6.6)	17.1 (7.1)	16.7 (8.8)	16.7 (7.5)	.97
UPDRS ADL score	5.4 (2.5)	6.1 (3.5)	5.2 (3.4)	5.3 (3.7)	.80
Hoehn and Yahr Scale score	1.9 (0.4)	1.8 (0.5)	1.8 (0.4)	1.9 (0.4)	.80
Schwab and England Scale score for ADL (examiner)	93.4 (3.0)	94.8 (4.0)	95.3 (3.4)	95.2 (4.4)	.47
Schwab and England Scale score for ADL (subject)	93.4 (4.4)	94.3 (4.6)	95.5 (3.6)	95.4 (4.2)	.39
Mini-Mental State Examination	29.1 (1.3)	29.3 (1.2)	29.0 (1.2)	29.2 (1.0)	.85
Timed tapping score	129.7 (21.5)	141.2 (32.3)	144.1 (28.0)	150.4 (29.1)	.17

*Unless otherwise indicated, data are given as mean (SD). UPDRS indicates Unified Parkinson's Disease Rating Scale; ADL, activities of daily living.

sensitive reduced form of nicotinamide adenine dinucleotide (NADH) cytochrome-c reductase. The electron transport activities were normalized to that of citrate synthetase to correct for any differences in mitochondrial mass. Comparisons of complex I and complex I/III activity at the baseline and final visits among patients treated with coenzyme Q₁₀ and placebo were made using analysis of covariance, adjusting for the baseline value and investigator as covariates.

All statistical analyses were performed using SAS software (Version 8; SAS Institute Inc, Cary, NC).

RESULTS

SUBJECTS ENROLLED

Eighty subjects were enrolled from May 24, 1999, through February 17, 2000 (Figure 1). At the baseline visit, the

groups were well matched for sex, age, severity of PD (the UPDRS and Hoehn and Yahr Scale scores and the timed tapping score), disability (the Schwab and England Scale score) and intellectual function (the Mini-Mental State Examination score) (Table 1). The characteristics of our subjects were very similar to those in previous studies enrolling subjects who did not have disability sufficient to require levodopa therapy.^{30,34} Three subjects prematurely terminated or were lost to follow-up from the study before the investigator determined that they had reached the point that their disability warranted use of levodopa (Figure 1). Increased tremor, lower-back pain, and increased nocturia developed in 1 subject who was receiving 1200 mg/d of coenzyme Q₁₀ and who prematurely terminated. This subject was noncompliant, and the investigator did not believe that the symptoms were

Table 2. Adverse Events Reported by at Least 4 Subjects

Adverse Event	Placebo Group, No. (%)	Coenzyme Q ₁₀ Groups, No. (%)			P Value*
		300 mg/d	600 mg/d	1200 mg/d	
All					
Arthralgia	1 (6.3)	1 (4.8)	0	2 (8.7)	.50
Back pain	1 (6.3)	2 (9.5)	1 (5.0)	4 (17.4)	.20
Coughing	1 (6.3)	1 (4.8)	1 (5.0)	1 (4.3)	.50
Diarrhea	0	2 (9.5)	1 (5.0)	2 (8.7)	.29
Dizziness	1 (6.3)	0	2 (10.0)	3 (13.0)	.15
Dyspepsia	0	1 (4.8)	2 (10.0)	2 (8.7)	.16
Fall	1 (6.3)	3 (14.3)	0	1 (4.3)	.25
Fatigue	1 (6.3)	2 (9.5)	1 (5.0)	0	.18
Flatulence	1 (6.3)	0	2 (10.0)	1 (4.3)	.50
Headache	1 (6.3)	1 (4.8)	2 (10.0)	3 (13.0)	.23
Hypercholesterolemia	2 (12.5)	1 (4.8)	0	1 (4.3)	.18
Infection, bacterial	0	3 (14.3)	0	1 (4.3)	.50
Infection, viral	2 (12.5)	4 (19.0)	4 (20.0)	2 (8.7)	.39
Myalgia	1 (6.3)	3 (14.3)	0	2 (8.7)	.46
Nausea	0	3 (14.3)	1 (5.0)	2 (8.7)	.39
Pain	2 (12.5)	0	0	2 (8.7)	.50
Pharyngitis	0	2 (9.5)	1 (5.0)	2 (8.7)	.29
Sinusitis	1 (6.3)	2 (9.5)	0	3 (13.0)	.39
Reported by at least 4 (5%) of subjects, excluding mild					
Viral infection	0	1 (4.8)	1 (5.0)	2 (8.7)	.18
Pharyngitis	0	1 (4.8)	1 (5.0)	2 (8.7)	.18
Sinusitis	0	2 (9.5)	0	2 (8.7)	.33
Reported by at least 4 (5%) of subjects, excluding unlikely related					
Flatulence	1 (6.3)	0	2 (10.0)	1 (4.3)	.50

*Determined by the Cochran-Armitage exact test for trend.

related to the study drug. This subject was lost to follow-up.

TOLERABILITY AND SAFETY

Coenzyme Q₁₀ was well tolerated; no dosage reductions were needed in any of the treatment groups. The percentages of subjects receiving coenzyme Q₁₀ who reported any adverse event (19 subjects [90%] for the 300-mg/d group; 12 [60%] for the 600-mg/d group; and 21 [91%] for the 1200-mg/d group) were not significantly different from that in the placebo group (13 subjects [81%]) ($P=.51$, Cochran-Armitage exact test for trend). Most adverse events were mild. Eighteen adverse events were experienced by 4 (5%) or more subjects (Table 2). When mild adverse events were excluded, 3 were experienced by at least 4 subjects, including viral infection, pharyngitis, and sinusitis. The differences among the treatment groups were not significant, and no significant trend by dosage was found in the number of subjects experiencing an adverse event.

Analysis of 84 possible high or low laboratory results revealed a nominally significant or marginally significant trend by dosage in 4, including high carbon dioxide levels ($P=.01$), high mean corpuscular hemoglobin concentration ($P=.08$), and high sodium ($P=.06$) and uric acid levels ($P=.08$). The ongoing evaluation of abnormal laboratory results during the study and the review at the completion of the study did not reveal these to be clinically significant.

Analysis of the data for weight, sitting and standing blood pressure, and heart rate did not show any sig-

nificant differences among the treatment groups (data not shown).

EFFICACY

The adjusted mean changes in the total UPDRS score from the baseline to the final visit (positive values indicate worsening) were +11.99 for the placebo group, +8.81 for the 300-mg/d group, +10.82 for the 600-mg/d group, and +6.69 for the 1200-mg/d group (Table 3). Our primary analysis was a test for a trend between dosage and the mean change in the UPDRS score, and $P=.09$ (2-sided) was significant according to our prespecified criteria. The difference in the change in the total UPDRS score between the placebo group and the 1200-mg/d group was 5.30 (95% confidence interval, 0.21-10.39). A prespecified secondary analysis was comparison of each active treatment group with the placebo group. The difference was significant for the 1200-mg/d group ($P=.04$) but not for the 300- ($P=.22$) or the 600-mg/d ($P=.66$) groups.

The reduction in the worsening of the total UPDRS score was the result of slowed decline in all 3 components of the UPDRS, ie, mental (part I), activities of daily living (part II), and motor (part III), with the greatest effect in part II (Table 3). The greatest reduction was seen at the highest dosage (1200 mg/d). Results for the placebo vs the combined drug groups were similar (data not shown).

We also found a reduction in the worsening on the Schwab and England Scale, as assessed by the examiner ($P=.04$) but not by the patient ($P=.81$). The discrep-

Table 3. Adjusted Mean Change From Baseline*

	Placebo Group (n = 16)	Coenzyme Q ₁₀ Groups			P Value†
		300 mg/d (n = 21)	600 mg/d (n = 20)	1200 mg/d (n = 23)	
Total UPDRS score	11.99 (7.99 to 15.99)	8.81 (5.42 to 12.20)	10.82 (7.39 to 14.26)	6.69 (3.49 to 9.89)	.09
UPDRS mental score	0.90 (0.42 to 1.37)	0.54 (0.14 to 0.95)	0.35 (-0.06 to 0.77)	0.33 (-0.05 to 0.72)	.06
UPDRS motor score	6.54 (3.56 to 9.51)	5.88 (3.38 to 8.39)	6.47 (3.93 to 9.01)	4.61 (2.24 to 6.97)	.35
UPDRS ADL score	4.74 (3.10 to 6.38)	2.54 (1.14 to 3.94)	4.02 (2.60 to 5.44)	1.62 (0.30 to 2.93)	.02
Hoehn and Yahr Scale score	0.02 (-0.13 to 0.18)	0.16 (0.03 to 0.29)	0.15 (0.01 to 0.28)	0.13 (0.01 to 0.26)	.39
Schwab and England Scale score for ADL (examiner)	-7.98 (-10.58 to -5.37)	-4.89 (-7.08 to -2.70)	-7.03 (-9.26 to -4.79)	-3.55 (-5.63 to -1.48)	.04
Schwab and England Scale score for ADL (subject)	-7.06 (-10.64 to -3.48)	-4.53 (-7.54 to -1.51)	-7.50 (-10.57 to -4.43)	-5.38 (-8.24 to -2.53)	.81
Timed tapping score	-13.17 (-21.82 to -4.51)	-5.06 (-12.26 to 2.13)	-8.99 (-16.30 to -1.68)	-10.32 (-17.23 to -3.42)	.97

*Changes are given as the last observation carried forward, and reported as adjusted (least squares) means (95% confidence intervals) from the analysis of covariance. Abbreviations are explained in the first footnote to Table 1.

†Determined by the test for trend, as specified in the analysis plan.

Table 4. Adjusted Mean Change From Baseline to 1 Month*

	Placebo Group (n = 16)	Coenzyme Q ₁₀ Groups			P Value†
		300 mg/d (n = 21)	600 mg/d (n = 20)	1200 mg/d (n = 23)	
Total UPDRS score	0.22 (-2.12 to 2.57)	1.35 (-0.63 to 3.34)	1.43 (-0.58 to 3.45)	0.42 (-1.45 to 2.29)	.99
UPDRS mental score	-0.22 (-0.54 to 0.11)	-0.29 (-0.57 to -0.01)	-0.15 (-0.44 to 0.14)	-0.27 (-0.53 to 0.00)	.98
UPDRS motor score	0.00 (-1.88 to 1.89)	1.54 (-0.05 to 3.12)	1.28 (-0.33 to 2.89)	1.29 (-0.21 to 2.79)	.42
UPDRS ADL score	0.52 (-0.41 to 1.44)	0.12 (-0.66 to 0.91)	0.37 (-0.43 to 1.17)	-0.66 (-1.40 to 0.09)	.07
Hoehn and Yahr Scale score	0.01 (-0.14 to 0.16)	0.04 (-0.09 to 0.16)	-0.02 (-0.16 to 0.11)	0.02 (-0.10 to 0.14)	.94
Schwab and England Scale score for ADL (examiner)	-0.12 (-1.44 to 1.19)	-0.57 (-1.67 to 0.54)	-0.53 (-1.65 to 0.60)	0.28 (-0.77 to 1.32)	.52
Schwab and England Scale score for ADL (subject)	-0.38 (-3.00 to 2.23)	-0.07 (-2.28 to 2.13)	-0.91 (-3.16 to 1.33)	-1.86 (-3.95 to 0.22)	.27
Timed tapping score	0.68 (-5.24 to 6.60)	2.42 (-2.50 to 7.34)	-5.04 (-10.19 to 0.11)	-0.53 (-5.25 to 4.18)	.36

*Changes are given as the last observation carried forward and reported as adjusted (least squares) means (95% confidence intervals) from the analysis of covariance. Abbreviations are explained in the first footnote to Table 1.

†Determined by means of the test for trend, as specified in the analysis plan.

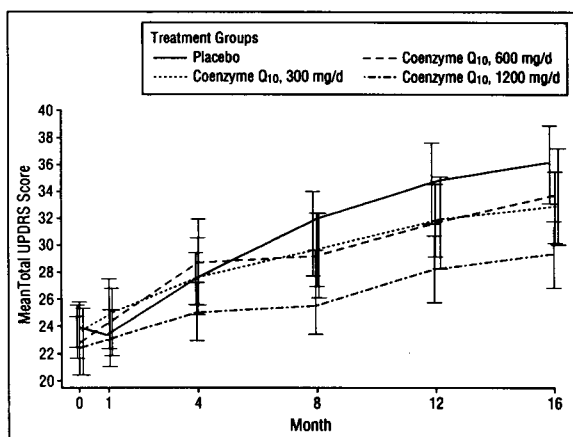


Figure 2. Unified Parkinson's Disease Rating Scale (UPDRS) scores. The scores for the total UPDRS (last observation carried forward) are expressed as mean (SEM). Higher scores indicate more severe features of Parkinson disease. Results of a test for a linear trend between the dosage and the mean change in the total UPDRS score indicated a trend for coenzyme Q₁₀ to reduce the increasing disability over time ($P=.09$). The score change for the 1200-mg/d coenzyme Q₁₀ group was significantly different from that of the placebo group ($P=.04$).

ancy between the results, as determined by the examiners and the patients, appeared to be primarily due to discordance between 1 subject, who was assigned to the 1200 mg/day treatment group, and the examiner. Coenzyme Q₁₀ did not have a significant effect on the scores for the Hoehn and Yahr Scale or the timed tapping task.

Examination of data at the month-1 visit indicated that coenzyme Q₁₀ did not have a significant effect on the total UPDRS score at that point (**Table 4**). However, at the 1-month visit, we noted benefit on part II of the UPDRS, particularly at the highest dosage.

Figure 2 shows the course of the total UPDRS scores across the 16 months of the study with the last observation carried forward. By the 8-month visit, the scores had clearly separated and established a pattern of the 300- and 600-mg/d groups being similar, with lower scores than those of the placebo group, and with the scores for the 1200-mg/d group being substantially lower than those of the other groups. This pattern persisted until the end of the study and was the result of similar changes in all 3 components of the UPDRS (**Figure 3**).

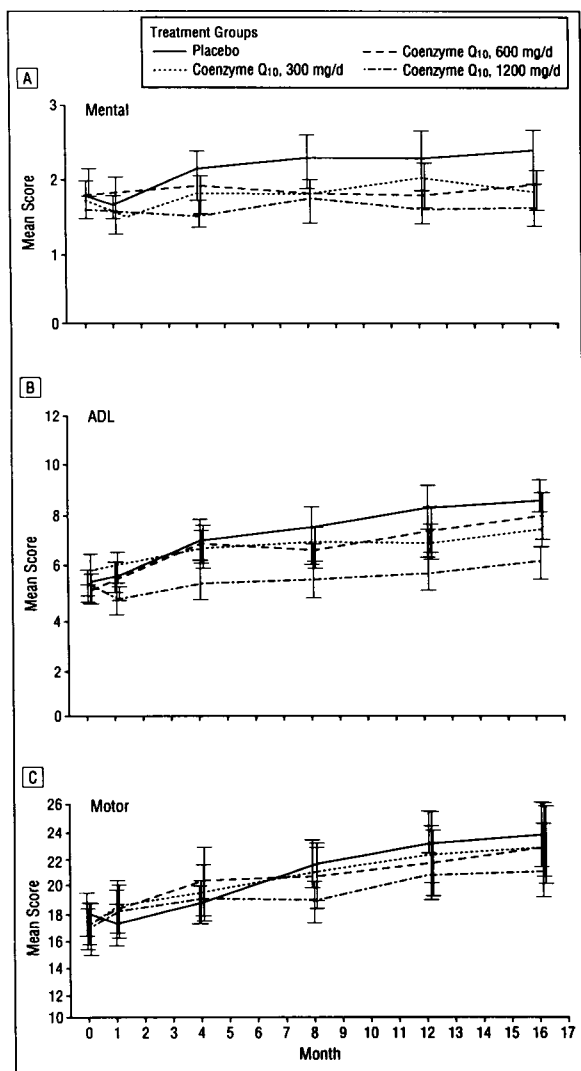


Figure 3. The 3 parts of the Unified Parkinson's Disease Rating Scale (UPDRS). The pattern of attenuation of the worsening of the total UPDRS score by coenzyme Q₁₀ was also seen in each of the 3 parts of the UPDRS (mental [part I; A], activities of daily living [ADL] [part II; B], and motor [part III; C], last observation carried forward).

Analyses of the area under the curve using the total UPDRS actual visit data showed similar, but not as significant, results (data not shown). Examination of the time until the subject was considered to need treatment with levodopa disclosed no significant effect of coenzyme Q₁₀ on this measure ($P=.43$) (**Figure 4**).

PLASMA LEVELS OF COENZYME Q₁₀

All groups receiving coenzyme Q₁₀ had highly significant increases in the mean plasma level of coenzyme Q₁₀ from baseline to the last visit (**Figure 5**) ($P<.001$), and the mean plasma levels of coenzyme Q₁₀ were significantly different among the 3 groups receiving active drug ($P<.05$), with the exception of the 300- and 600-mg/d groups ($P=.15$). All subjects received 1200 IU of vitamin E daily, and in each treatment group the plasma level

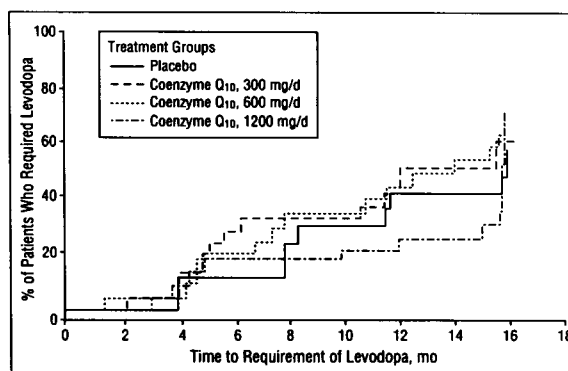


Figure 4. Percentage of patients who required levodopa by the time until the investigator considered that the subject needed treatment with levodopa.

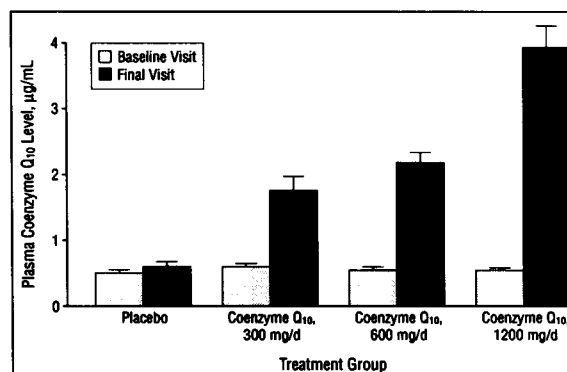


Figure 5. Plasma coenzyme Q₁₀ levels. In all groups treated with coenzyme Q₁₀, the plasma level at the last visit was significantly different from that at the baseline visit ($P<.001$), and the plasma levels of coenzyme Q₁₀ in the 3 groups receiving active drug were significantly different from each other ($P<.05$), with the exception of the 300- and 600-mg/d groups ($P=.15$). Samples (numbers of patients) available from the baseline/final visits were 13/14 for the placebo group, 19/19 for the 300-mg/d group, 16/17 for the 600-mg/d group, and 22/18 for the 1200-mg/d group.

of vitamin E increased slightly more than 2-fold (data not shown).

MITOCHONDRIAL ASSAYS

Results of the assay of the activity of complex I normalized to the activity of citrate synthetase did not indicate a significant effect of coenzyme Q₁₀ ($P=.73$). In this assay, the activity of complex I did not depend on endogenous coenzyme Q₁₀, as an excess of exogenous coenzyme Q₁ was added (**Figure 6A**). We also determined the activity of the electron transport chain from NADH to cytochrome-c reductase (complexes I and III), which did depend on the endogenous coenzyme Q₁₀, and found a significant increase in the activity of the electron transport chain with treatment with coenzyme Q₁₀ ($P=.04$) (**Figure 6B**).

CONCLUSION

Our dosage-ranging study found that coenzyme Q₁₀ was safe and well tolerated at the dosages of 300 to 1200 mg/d and that the 1200-mg/d dosage was associated with significant slowing of the worsening of PD as measured by

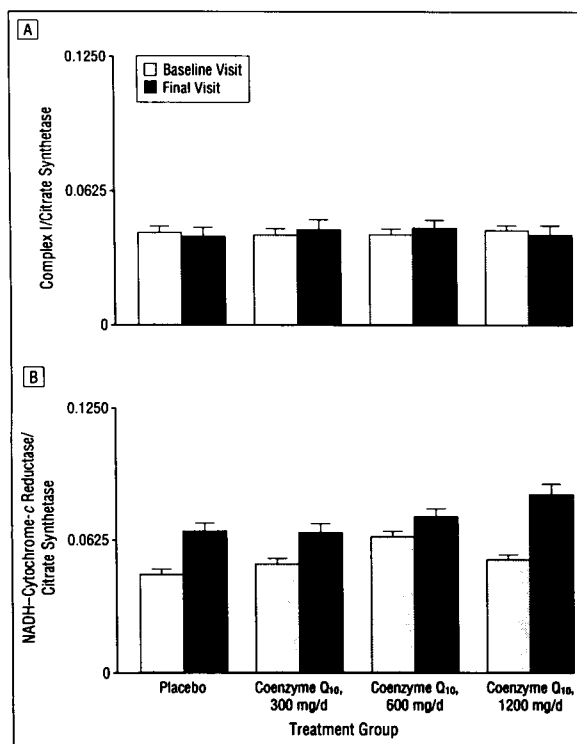


Figure 6. Mitochondrial activity. Assays were normalized to citrate synthetase to correct for differences in mitochondrial mass. A, Complex I activity, which is not dependent on endogenous coenzyme Q₁₀, did not differ among the treatment groups. B, The assay of the reduced form of nicotinamide adenine dinucleotide (NADH) to cytochrome-c reductase, which is dependent on the endogenous level of coenzyme Q₁₀, showed a significant trend for treatment with coenzyme Q₁₀. Samples (numbers of patients) available from the baseline/final visits were 12/14 for the placebo group, 18/21 for the 300-mg/d group, 19/17 for the 600-mg/d group, and 20/21 for the 1200-mg/d group for the complex I/citrate synthetase; and 12/14 for the placebo group, 19/21 for the 300-mg/d group, 19/17 for the 600-mg/d group, and 20/20 for the 1200-mg/d group for NADH to cytochrome-c reductase.

the total UPDRS score. The benefit was seen in all 3 of the components of the UPDRS, but the effect was greatest in part II (activities of daily living). Consistent with the effect on part II, we found a significant effect on the Schwab and England Scale score as judged by the examiner.

The effect of coenzyme Q₁₀ on our primary response variable, change in total UPDRS score, was not paralleled by the time to disability requiring treatment with levodopa. However, the group treated with 1200 mg/d tended to reach this end point more slowly until the end of the study. We were not surprised by this discrepancy. Analysis of the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) Study³⁰ suggested that the time to levodopa treatment would be a less informative measure than the change in total UPDRS score in a 16-month study (D.O., unpublished data, 1994), thus prompting exploration of the current trial design for phase 2 trials.

The mechanism(s) through which coenzyme Q₁₀ exerted its beneficial effect cannot be determined from our clinical trial, but our data are consistent with an effect on mitochondrial function. The assay of NADH to cytochrome-c reductase activity, which relies on endoge-

nous coenzyme Q₁₀, demonstrated a significant increase in activity in subjects taking 1200 mg/d of coenzyme Q₁₀. Although the results of our study of mitochondrial activity in platelets do not prove that a similar benefit occurred in the brain, the results are consistent with this possibility. Our data are consistent with the hypothesis that mitochondrial dysfunction plays a role in the pathogenesis of PD and that treatments targeted at mitochondria might ameliorate the functional decline in PD.

Coenzyme Q₁₀ was unlikely to exert its effect through an increase in the level of nigrostriatal dopamine. In preclinical studies, supplementation of the diet of 1-year-old mice with coenzyme Q₁₀ (200 mg/kg per day) for 5 weeks did not affect striatal levels of dopamine or its metabolites.²⁰

Investigators have previously described improvement after supplemental coenzyme Q₁₀ treatment in small case series in which the patients appeared to have an inherited deficiency of coenzyme Q₁₀.³⁵⁻³⁸ Similarly, oral coenzyme Q₁₀ treatment (600 mg/d) for 3 months in patients with Friedreich ataxia improved bioenergetics in cardiac and skeletal muscle, but after 6 months of treatment, neurological function was not improved.³⁹

The effect of coenzyme Q₁₀ in other diseases, particularly neurological disorders, has been inconsistent. There have been numerous reports of the benefits of coenzyme Q₁₀ in patients with heart disease, but the studies were often not controlled.⁴⁰ A recent prospective, randomized, double-blinded, placebo-controlled trial of coenzyme Q₁₀ in congestive heart failure did not show benefit, but the dosage (200 mg/d) may not have been adequate.⁴¹ Previous studies in a variety of muscular disorders have had inconsistent results.⁴²⁻⁴⁵ The dosages used (30-300 mg/d) may have been inadequate, and heterogeneous neurological disorders were often studied together in these trials. In the present study, the strict inclusion criteria maximized the likelihood that the subjects had idiopathic PD.⁴⁶

Consistent with our findings of a reduction in the functional decline in PD are the results of a trial in which patients with early Huntington disease received coenzyme Q₁₀ (600 mg/d), remacemide hydrochloride (600 mg/d), a combination of remacemide and coenzyme Q₁₀, or placebo.⁴⁷ The decline in total functional capacity was not significantly altered by any of the treatments, but subjects receiving coenzyme Q₁₀ (with or without remacemide treatment) showed 13% less decline in total functional capacity than did the subjects who did not receive coenzyme Q₁₀ ($P = .15$). Previous studies in patients with Huntington disease showed that coenzyme Q₁₀ significantly lowered increased lactate levels in the cerebral cortex, demonstrating that it exerts biological effects in the brain.⁴⁸

Results of our study, in which the greatest benefit was found at a dosage of 1200 mg/d, the study of Huntington disease, in which an intriguing trend toward benefit at a dosage of 600 mg/d was observed, and the congestive heart failure study, in which no benefit was seen at a dosage of 200 mg/d, indicate that the dosage of coenzyme Q₁₀ may be crucial. The beneficial trend in our trial was driven by the effect seen at the highest dosage of coenzyme Q₁₀ (1200 mg/d). The plasma levels of coenzyme Q₁₀ in the groups receiving 300 and 600 mg/d

Parkinson Study Group

Steering Committee

Clifford W. Shults, MD (principal investigator, University of California–San Diego and Veterans Affairs San Diego Healthcare System); David Oakes, PhD (chief biostatistician, University of Rochester, Rochester, NY); Karl Kieburtz, MD (director, Clinical Trials Coordination Center, University of Rochester); M. Flint Beal, MD (director, Neurochemistry Laboratory, Weill Medical College of Cornell University, New York, NY); Richard Haas, MB Chir (director, Mitochondrial Research Laboratory, University of California–San Diego); Sandy Plumb, BS (chief study coordinator, University of Rochester); Jorge L. Juncos, MD (Emory University, Atlanta, Ga); John Nutt, MD (Oregon Health and Science University, Portland); and Ira Shoulson, MD (University of Rochester).

Scientific Advisory Committee

Chris Goetz, MD (chair, Rush Presbyterian/St Luke's Medical Center, Chicago, Ill), and Walter Koroshetz, MD (Massachusetts General Hospital, Boston).

Investigators

Julie Carter, RN, MS, ANP (Oregon Health and Science University); Katie Kompoliti, MD (Rush Presbyterian/St Luke's Medical Center); Joel S. Perlmutter, MD (Washington University, St Louis, Mo); Stephen Reich, MD (The Johns Hopkins University, Baltimore, Md); Matthew Stern, MD (University of Pennsylvania, Philadelphia); Ray L. Watts, MD (Emory University); Roger Kurlan, MD (University of Rochester); Eric Molho, MD (Albany Medical College, Albany, NY); Madaline Harrison, MD (University of Virginia, Charlottesville); and Mark Lew, MD (University of Southern California, Los Angeles).

Coordinators

Barbara Alexander-Brown, BS, CRA (Oregon Health and Science University); Kim Janko, RN, BSN (Rush Presbyterian/St Luke's Medical Center); Lori McGee-Minnich, RN, BSN (Washington University); Becky Dunlop, RN, BSN (The Johns Hopkins University); Sue Reichwein, BASW (University of Pennsylvania); Colleen Peach, RN, MSN (Emory University); Nancy Pearson, RN, MSN (University of Rochester); Sharon Evans, RN (Albany Medical College); Elke Rost-Ruffner, RN, BSN (University of Virginia); and Connie Kawai, RN (University of Southern California).

Clinical Trials Coordination Center

Giovanni Schiffrino, MD, Elaine Julian-Baros, Karen Hodgeman, Connie Orme, BA, Larry Preston, BPS, and Karen Rothenburgh (University of Rochester); Lin Zhang, MD (University of California–Davis).

Biostatistics Center

Janice Bausch, BA, and Shirley Eberly, MS (University of Rochester).

Pharmacy Center

Steven Bean, RPh (University of Rochester).

Safety Monitoring Committee

Pierre Tariot, MD, and Jack Hall, PhD (University of Rochester); Robert Rodnitzky, MD (The University of Iowa, Iowa City).

were relatively close, as were the total UPDRS scores in both groups. The plasma and presumably brain levels of coenzyme Q₁₀ may be a significant determinant of the effectiveness of the treatment.

To our knowledge, our study is the first trial to systematically explore the safety and efficacy of high dosages of coenzyme Q₁₀. Our data suggest that in treatment of neurological disorders in which evidence of complex I or II dysfunction are found, such as PD and Huntington disease, dosages much higher than those previously used may be required. The benefit was greatest in the group receiving the highest dosage, 1200 mg/d. It is conceivable that a greater effect could be seen at even higher dosages of coenzyme Q₁₀. Future studies of coenzyme Q₁₀ in PD and other disorders will need to explore the effect of dosages of 1200 mg/d and higher.

CONCLUSIONS

In our study, coenzyme Q₁₀ treatment at high dosages was safe and well tolerated and reduced the worsening of PD, as reflected in the total UPDRS score. It would be premature to recommend the use of coenzyme Q₁₀ for the treatment of PD. Our results need to be confirmed in a larger, phase 3 study, and the appropriate dosage and the magnitude of effect need to be better defined.

Accepted for publication June 5, 2002.

From the Department of Neurosciences, University of California–San Diego, La Jolla (Drs Shults and Haas); Veterans Affairs San Diego Healthcare System, San Diego (Dr Shults); Departments of Biostatistics (Dr Oakes) and Neurology (Drs Kieburtz, Shoulson, and Kurlan and Ms Plumb), University of Rochester School of Medicine and Dentistry, Rochester, NY; Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY (Dr Beal); Department of Neurology and Wesley Woods Center, Emory University, Atlanta, Ga (Drs Juncos and Watts); Parkinson's Disease Research, Education and Clinical Center–Veterans Affairs Medical Center (Dr Nutt) and Oregon Health and Science University (Dr Nutt and Ms Carter), Portland; and the Departments of Neurology, Rush Presbyterian/St. Luke's Medical Center, Chicago, Ill (Dr Kompoliti), Washington University, St. Louis, Mo (Dr Perlmutter), The Johns Hopkins University, Baltimore, Md (Dr Reich), University of Pennsylvania and Parkinson's Disease Research, Education and Clinical Center–Veterans Affairs Medical Center, Philadelphia (Dr Stern), Albany Medical College, Albany, NY (Dr Molho), University of Virginia, Charlottesville (Dr Harrison), and University of Southern California, Los Angeles (Dr Lew). The complete list of the Parkinson Study Group members is listed in the box on this page. Dr Shults and Mr Meese are coinventors in a pending patent application. The application is jointly owned by Enzymatic Therapy, Inc, Green Bay, Wis (owner of Vitaline Corp, Ashland, Ore), and The Regents of the University of California.

Author contributions: Study concept and design (Drs Shults, Oakes, Kieburtz, Beal, Haas, Nutt, Shoulson, and Watts); acquisition of data (Drs Shults, Beal, Haas, Kompoliti, Perlmutter, Reich, Stern, Watts, Kurlan, Molho, Harrison, and Lew and Mss Plumb and Carter); analysis and interpretation of data (Drs Shults, Oakes, Kieburtz, Beal, Haas, Juncos, Shoulson, and Molho and Ms Plumb); drafting of the manuscript (Drs Shults, Oakes, and Shoulson); critical revision of the manuscript for im-

portant intellectual content (Drs Shults, Oakes, Kiebertz, Beal, Haas, Juncos, Nutt, Shoulson, Kompoliti, Perlmutter, Reich, Stern, Watts, Kurlan, Molho, Harrison, and Lew and Ms Plumb and Carter); statistical expertise (Dr Oakes); obtained funding (Drs Shults, Oakes, Kiebertz, and Shoulson); administrative, technical, and material support (Drs Shults, Kiebertz, Beal, Haas, Shoulson, Perlmutter, Watts, Kurlan, and Harrison and Ms Plumb); and study supervision (Drs Shults, Oakes, Beal, Juncos, Perlmutter, and Stern and Ms Plumb).

This study was supported by grant R01 NS36714 from the National Institutes of Health, Bethesda, Md (Dr Shults). The coenzyme Q₁₀ and placebo used in the study were formulated into wafers and packaged without charge by Vitaline Corp, Ashland, Ore.

We thank the National Institute of Neurological Disorders and Stroke for support of the study, particularly Eugene Oliver, PhD (Program Director for the study), and the National Institute of Neurological Disorders and Stroke—Constituted Performance and Safety Monitoring Board (E. Clarke Haley, MD; David Eidelberg, MD; Constantine Gatsonis, PhD; and Walter Rocca, MD, MPH). Dr Shults especially thanks Stephanie Shanks, Riak Akuei and Myra Kosak for administrative oversight of the study and Aileen Shinaman, JD, Parkinson Study Group Executive Director, for her support during the study. We also acknowledge the contribution of Thuy Le, PhD, for mitochondrial assays and Beverly Lorenzo and Linda Metakis for assays of coenzyme Q₁₀ levels.

Corresponding author and reprints: Clifford W. Shults, MD, Department of Neurosciences, Mail Code 0662, University of California—San Diego, 9500 Gilman Dr, La Jolla, CA 92093-0662 (e-mail: cshults@ucsd.edu).

REFERENCES

- Tanner CM, Goldman SM. Epidemiology of Parkinson's disease. *Neurol Clin*. 1996; 14:317-335.
- Braak H, Braak E. Pathoanatomy of Parkinson's disease. *J Neurol*. 2000;247 (suppl 2):113-1110.
- Forno LS. Neuropathology of Parkinson's disease. *J Neuropathol Exp Neurol*. 1996;55:259-272.
- Olanow CW, Tatton WG. Etiology and pathogenesis of Parkinson's disease. *Annu Rev Neurosci*. 1999;22:123-144.
- Vaughan JR, Davis MB, Wood NW. Genetics of parkinsonism: a review. *Ann Hum Genet*. 2001;65(pt 2):111-126.
- Sherer TB, Betarbet R, Greenamyre JT. Pathogenesis of Parkinson's disease. *Curr Opin Invest Drugs*. 2001;2:657-662.
- Langston JW, Ballard P, Tetrad JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science*. 1983;219:979-980.
- Przedborski S, Jackson-Lewis V. Mechanisms of MPTP toxicity. *Mov Disord*. 1998; 13(suppl 1):35-38.
- Schapiro AH, Mann VM, Cooper JM, et al. Anatomic and disease specificity of NADH CoQ1 reductase (complex I) deficiency in Parkinson's disease. *J Neurochem*. 1990;55:2142-2145.
- Turner C, Schapiro AH. Mitochondrial dysfunction in neurodegenerative disorders and ageing. *Adv Exp Med Biol*. 2001;487:229-251.
- Parker WD Jr, Boyson SJ, Parks JK. Abnormalities of the electron transport chain in idiopathic Parkinson's disease. *Ann Neurol*. 1989;26:719-723.
- Krige D, Carroll MT, Cooper JM, Marsden CD, Schapiro AH. Platelet mitochondrial function in Parkinson's disease. *Ann Neurol*. 1992;32:782-788.
- Yoshino H, Nakagawa-Hattori Y, Kondo T, Mizuno Y. Mitochondrial complex I and II activities of lymphocytes and platelets in Parkinson's disease. *J Neural Transm*. 1992;4:27-34.
- Bencke R, Strümpfer P, Weiss H. Electron transfer complexes I and IV of platelets are abnormal in Parkinson's disease but normal in Parkinson-plus syndromes. *Brain*. 1993;116:1451-1463.
- Haas R, Nasirian F, Nakano K, et al. Low platelet mitochondrial complex I and complex II/III activity in early untreated Parkinson's disease. *Ann Neurol*. 1995; 37:714-722.
- Shults CW, Nasirian F, Ward DM, et al. Carbidopa/levodopa and selegiline do not affect platelet mitochondrial function in early parkinsonism. *Neurology*. 1995; 45:344-348.
- Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci*. 2000;3:1301-1306.
- Shults CW, Haas RH, Passov D, Beal MF. Coenzyme Q₁₀ levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and non-parkinsonian subjects. *Ann Neurol*. 1997;42:261-264.
- Matsubara T, Azuma T, Yoshida S, Yamagami T. Serum coenzyme Q₁₀ level in Parkinson syndrome. In: Folkers K, Littarru GP, Yamagami T, eds. *Biomedical and Clinical Aspects of Coenzyme Q*. New York, NY: Elsevier Science Publishers; 1991:159-166.
- Beal MF, Matthews RT, Tieleman A, Shults CW. Coenzyme Q₁₀ attenuates the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced loss of striatal dopamine and dopaminergic axons in aged mice. *Brain Res*. 1998;783:109-114.
- Matthews RT, Yang L, Browne S, Baik M, Beal MF. Coenzyme Q₁₀ administration increases brain mitochondrial concentrations and exerts neuroprotective effects. *Proc Natl Acad Sci U S A*. 1998;95:8892-8897.
- Shults CW, Beal MD, Fontaine S, Nakano K, Haas RH. Absorption, tolerability and effects on mitochondrial activity of oral coenzyme Q₁₀ in parkinsonian patients. *Neurology*. 1998;50:793-795.
- Folstein MF, Folstein SE, McHugh P. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:129-138.
- Hamilton MA. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1988; 45:742-747.
- Lang AE. Clinical rating scales and videotape analysis. In: Koller WC, Paulson G, eds. *Therapy of Movement Disorders*. 2nd ed. New York, NY: Marcel Dekker Inc; 1995:21-46.
- Martinez-Martin P, Gil-Nagel A, Gracia LM, et al. Unified Parkinson's Disease Rating Scale characteristics and structure. *Mov Disord*. 1994;9:76-83.
- Goetz CG, Stebbins GT, Chmura TA, Fahn S, Klawans HL, Marsden CD. Teaching tape for the motor section of the Unified Parkinson's Disease Rating Scale. *Mov Disord*. 1995;10:263-266.
- Richards M, Marder K, Cote L, Mayeux R. Interrater reliability of the Unified Parkinson's Disease Rating Scale. *Mov Disord*. 1994;9:89-91.
- Fleiss JL. *Statistical Methods for Rates and Proportions*. 2nd ed. New York, NY: John Wiley & Sons Inc; 1981:138-159.
- Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. 1989;321:1364-1371.
- Lee YJ, Ellenberg JH, Hirtz DG, Nelson KB. Analysis of clinical trials by treatment actually received: is it really an option? *Stat Med*. 1991;10:1595-1605.
- Parkinson Study Group. Safety and efficacy of pramipexole in early Parkinson's disease. *JAMA*. 1997;278:125-130.
- Cox DR, Oakes D. *Analysis of Survival Data*. New York, NY: Chapman & Hall; 1984.
- Parkinson Study Group. A controlled trial of lazabemide (RO19-6327) in untreated Parkinson's disease. *Ann Neurol*. 1993;33:350-356.
- Ogasahara S, Engel AG, Frens D, Mack D. Muscle coenzyme Q deficiency in familial mitochondrial encephalopathy. *Proc Natl Acad Sci U S A*. 1989;86:2379-2382.
- Hirano M, Sobreira C, Shanske S, et al. Coenzyme Q₁₀ deficiency in a woman with myopathy, recurrent myoglobinuria and seizures [abstract]. *Neurology*. 1996; 46(suppl 2):A231.
- Musumeci O, Naini A, Slonim AE, et al. Familial cerebellar ataxia with muscle coenzyme Q₁₀ deficiency. *Neurology*. 2001;56:849-855.
- Di Giovanni S, Mirabella M, Spinazzola A, et al. Coenzyme Q₁₀ reverses clinical and biochemical impairment and reduces apoptotic features in familial CoQ₁₀ deficiency. *Neurology*. 2001;57:515-518.
- Lodi R, Hart PE, Rajagopalan B, et al. Antioxidant treatment improves in vivo cardiac and skeletal muscle bioenergetics in patients with Friedreich's ataxia. *Ann Neurol*. 2001;49:590-596.
- Tran MT, Mitchell TM, Kennedy DT, Giles JT. Role of coenzyme Q₁₀ in chronic heart failure, angina, and hypertension. *Pharmacotherapy*. 2001;21:797-806.
- Khatta M, Alexander BS, Krichen CM, et al. The effect of coenzyme Q₁₀ in patients with congestive heart failure. *Ann Intern Med*. 2000;132:636-640.
- Bresolin N, Doriguzzi C, Ponzetto C, et al. Ubidecarenone in the treatment of mitochondrial myopathies: a multi-center double-blind trial. *J Neurol Sci*. 1990; 100:70-78.
- Zierz S, von Wersebe O, Bleistein J, Jerusalem F. Exogenous coenzyme Q (CoQ) fails to increase CoQ in skeletal muscle of two patients with mitochondrial myopathies. *J Neurol Sci*. 1990;95:283-290.
- Matthews PM, Ford B, Dandurand RJ, et al. Coenzyme Q₁₀ with multiple vitamins is generally ineffective in treatment of mitochondrial disease. *Neurology*. 1993;43:884-890.
- Peterson PL. The treatment of mitochondrial myopathies and encephalomyopathies. *Biochim Biophys Acta*. 1995;1271:275-280.
- Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. *Neurology*. 1992;42:1142-1146.
- Huntington Study Group. A randomized, placebo-controlled trial of coenzyme Q₁₀ and remacemide in Huntington's disease. *Neurology*. 2001;57:397-404.
- Koroshetz WJ, Jenkins BG, Rosen BR, Beal MF. Energy metabolism defects in Huntington's disease and effects of coenzyme Q₁₀. *Ann Neurol*. 1997;41:160-165.