ORIGINAL CONTRIBUTION

Effects of Coenzyme Q_{10} in Early Parkinson Disease

Evidence of Slowing of the Functional Decline

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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 Q_{10} 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 Q_{10} 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 Q_{10} was safe and well tolerated at dosages of up to 1200 mg/d. Less disability developed in subjects assigned to coenzyme Q_{10} than in those assigned to placebo, and the benefit was greatest in subjects receiving the highest dosage. Coenzyme Q_{10} appears to slow the progressive deterioration of function in PD, but these results need to be confirmed in a larger study.

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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 mitochondrial electron transport chain stimulated studies of mitochondrial function in PD.[7,8] Schapira et al[9] and Turner and Schapira[10] reported a selective decrease in

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complex I activity in the postmortem substantia nigra in patients with PD. Parker et al[11] first reported and others confirmed[12-14] 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-

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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 Q_{10} is the electron acceptor for complexes I and II and also a potent antioxidant. Shults et al[18] demonstrated reduced levels of coenzyme Q_{10} in the mitochondria isolated from platelets of patients with PD, and the serum level of coenzyme Q_{10} in patients with parkinsonism has been reported to be significantly lower than that in age-comparable patients with stroke.[19] Beal et al[20] demonstrated that oral supplementation with coenzyme Q_{10} reduced the loss of dopamine and dopaminergic axons in the striatum in 1-year-old mice treated with MPTP. Matthews et al[21] found that oral supplementation with coenzyme Q_{10} in rats resulted in significant increases in the concentration of coenzyme Q_{10} in mitochondria in the cerebral cortex. In a pilot study, Shults et al[22] demonstrated that oral consumption of coenzyme Q_{10} 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 Q_{10}. On the basis of this work, we undertook a dosage-ranging study to evaluate the safety and tolerability of high dosages of coenzyme Q_{10} in patients with early PD and the ability of coenzyme Q_{10} 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 Q_{10} 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 Q_{10} 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 Q_{10} in plasma.[22] On completion of the baseline visit, each patient was randomly assigned to receive coenzyme Q_{10} 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 Q_{10}. 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 Q_{10} 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 Q_{10} 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 agonists, 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 Q_{10} 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 Q_{10} 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 Q_{10}

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 Q_{10} were performed by means of techniques previously described with modification.[18] The values from 1 subject, who was assigned to receive coenzyme Q_{10} 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 Q_{10} 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-

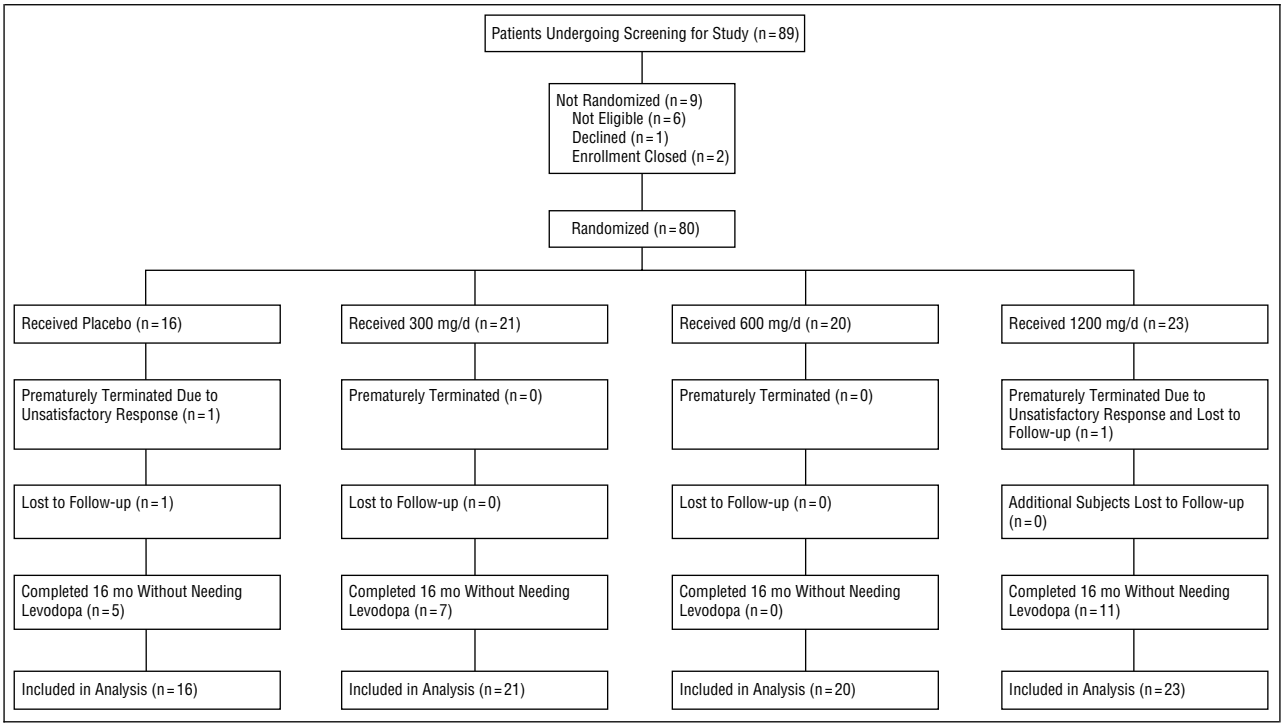

Figure 1. Patient flowchart.

Table 1. Baseline Characteristics*

	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)	
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 dincleotide (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 Q_{10} 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 Q_{10} 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 Q_{10} was well tolerated; no dosage reductions were needed in any of the treatment groups. The percentages of subjects receiving coenzyme Q_{10} 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 significant 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 300 mg/d (n = 21)	600 mg/d (n = 20)	1200 mg/d (n = 23)	*P* Value†
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 (–.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 300 mg/d (n = 21)	600 mg/d (n = 20)	1200 mg/d (n = 23)	*P* Value†
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.

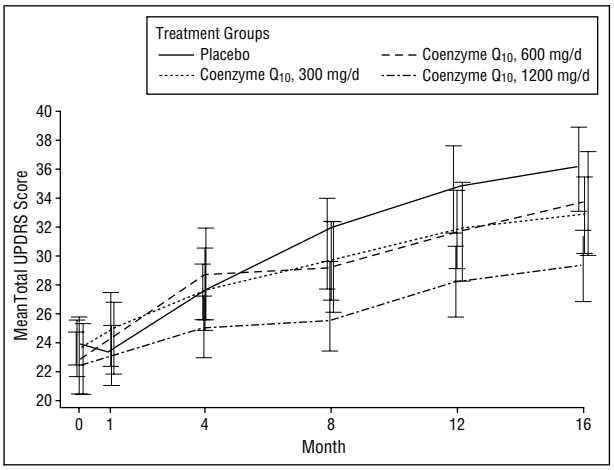

Figure 2. Unified Parkinson's Disease Rating Scale (UPDRS) scores. The scores for the total UPDRS (last observation carried forward) are expressed as mean (SEM). Higher scores indicate more severe features of Parkinson disease. Results of a test for a linear trend between the dosage and the mean change in the total UPDRS score indicated a trend for coenzyme Q_{10} to reduce the increasing disability over time (P=.09). The score change for the 1200-mg/d coenzyme Q_{10} 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 Q_{10} 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 Q_{10} 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**).

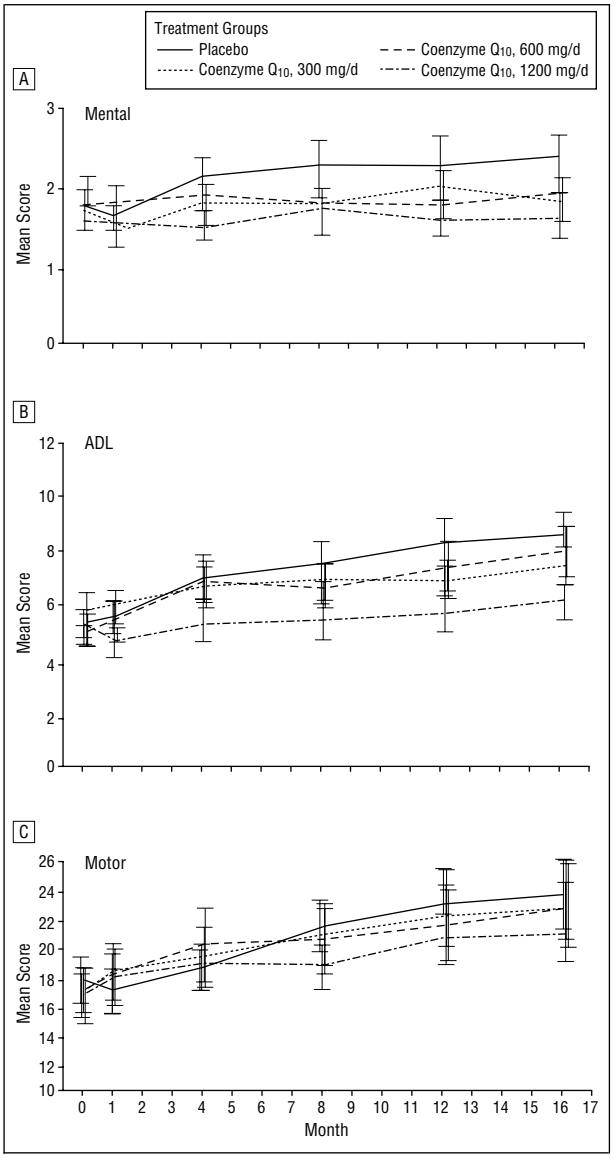

Figure 3. The 3 parts of the Unified Parkinson's Disease Rating Scale (UPDRS). The pattern of attenuation of the worsening of the total UPDRS score by coenzyme Q_{10} was also seen in each of the 3 parts of the UPDRS (mental [part I; A], activities of daily living [ADL] [part II; B], and motor [part 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 Q_{10} on this measure ($P=.43$) (**Figure 4**).

PLASMA LEVELS OF COENZYME Q_{10}

All groups receiving coenzyme Q_{10} had highly significant increases in the mean plasma level of coenzyme Q_{10} from baseline to the last visit (**Figure 5**) ($P<.001$), and the mean plasma levels of coenzyme Q_{10} 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

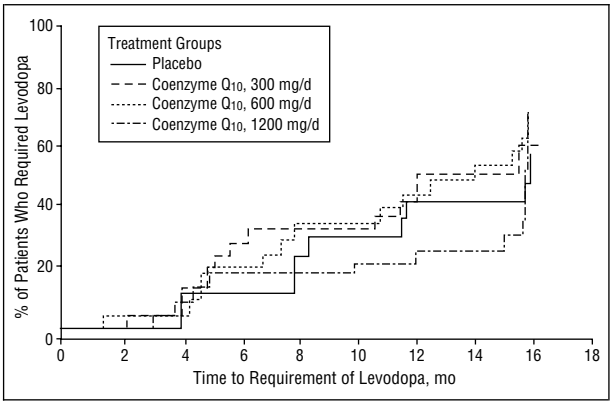

Figure 4. Percentage of patients who required levodopa by the time until the investigator considered that the subject needed treatment with levodopa.

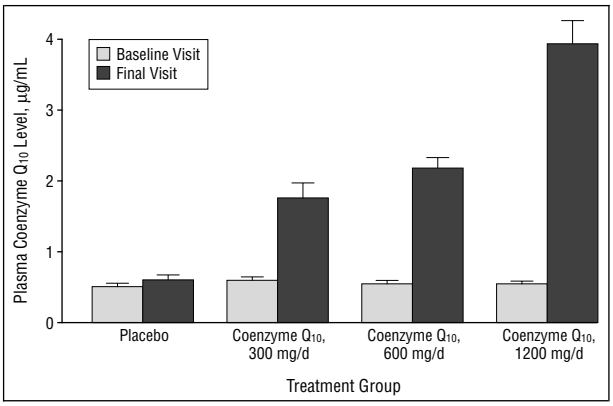

Figure 5. Plasma coenzyme Q_{10} levels. In all groups treated with coenzyme Q_{10}, the plasma level at the last visit was significantly different from that at the baseline visit ($P<.001$), and the plasma levels of coenzyme Q_{10} in the 3 groups receiving active drug were significantly different from 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 Q_{10} ($P=.73$). In this assay, the activity of complex I did not depend on endogenous coenzyme Q_{10}, as an excess of exogenous coenzyme Q_1 was added (**Figure 6**A). 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 Q_{10}, and found a significant increase in the activity of the electron transport chain with treatment with coenzyme Q_{10} ($P=.04$) (Figure 6B).

COMMENT

Our dosage-ranging study found that coenzyme Q_{10} 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

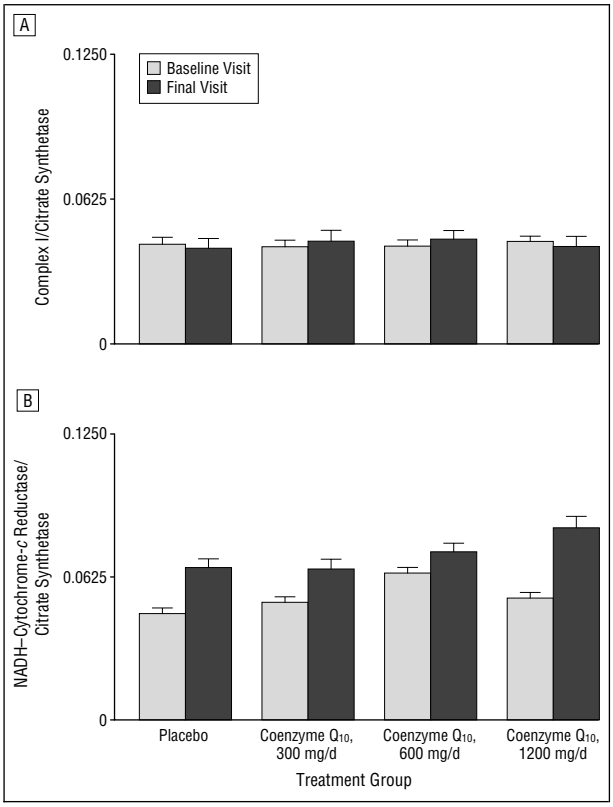

Figure 6. Mitochondrial activity. Assays were normalized to citrate synthetase to correct for differences in mitochondrial mass. A, Complex I activity, which is not dependent on endogenous coenzyme Q_{10}, did not differ among the treatment groups. B, The assay of the reduced form of nicotinamide adenine dincleotide (NADH) to cytochrome-*c* reductase, which is dependent on the endogenous level of coenzyme Q_{10}, showed a significant trend for treatment with coenzyme Q_{10}. 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 Q_{10} 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) Study[30] 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 Q_{10} 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 endogenous coenzyme Q_{10}, demonstrated a significant increase in activity in subjects taking 1200 mg/d of coenzyme Q_{10}. 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 Q_{10} 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 Q_{10} (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 Q_{10} treatment in small case series in which the patients appeared to have an inherited deficiency of coenzyme Q_{10}.[35-38] Similarly, oral coenzyme Q_{10} 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 Q_{10} in other diseases, particularly neurological disorders, has been inconsistent. There have been numerous reports of the benefits of coenzyme Q_{10} in patients with heart disease, but the studies were often not controlled.[40] A recent prospective, randomized, double-blinded, placebo-controlled trial of coenzyme Q_{10} 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 Q_{10} (600 mg/d), remacemide hydrochloride (600 mg/d), a combination of remacemide and coenzyme Q_{10}, or placebo.[47] The decline in total functional capacity was not significantly altered by any of the treatments, but subjects receiving coenzyme Q_{10} (with or without remacemide treatment) showed 13% less decline in total functional capacity than did the subjects who did not receive coenzyme Q_{10} ($P=.15$). Previous studies in patients with Huntington disease showed that coenzyme Q_{10} 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 Q_{10} may be crucial. The beneficial trend in our trial was driven by the effect seen at the highest dosage of coenzyme Q_{10} (1200 mg/d). The plasma levels of coenzyme Q_{10} in the groups receiving 300 and 600 mg/d

Parkinson Study Group

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were relatively close, as were the total UPDRS scores in both groups. The plasma and presumably brain levels of coenzyme Q_{10} 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 Q_{10}. 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 Q_{10}. Future studies of coenzyme Q_{10} in PD and other disorders will need to explore the effect of dosages of 1200 mg/d and higher.

CONCLUSIONS

In our study, coenzyme Q_{10} 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 Q_{10} 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.

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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, Kieburtz, Beal, Haas, Juncos, Nutt, Shoulson, Kompoliti, Perlmutter, Reich, Stern, Watts, Kurlan, Molho, Harrison, and Lew and Mss Plumb and Carter); *statistical expertise* (Dr Oakes); *obtained funding* (Drs Shults, Oakes, Kieburtz, and Shoulson); *administrative, technical, and material support* (Drs Shults, Kieburtz, 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).

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