



CoQ10 in progressive supranuclear palsy: A randomized, placebo-controlled, double-blind trial

Citation

Apetauerova, Diana, Stephanie A. Scala, Robert W. Hamill, David K. Simon, Subash Pathak, Robin Ruthazer, David G. Standaert, and Talene A. Yacoubian. 2016. "CoQ10 in progressive supranuclear palsy: A randomized, placebo-controlled, double-blind trial." *Neurology® Neuroimmunology & Neuroinflammation* 3 (5): e266. doi:10.1212/NXI.0000000000000266. <http://dx.doi.org/10.1212/NXI.0000000000000266>.

Published Version

doi:10.1212/NXI.0000000000000266

Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:29002466>

Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

Share Your Story

The Harvard community has made this article openly available.
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

CoQ10 in progressive supranuclear palsy

A randomized, placebo-controlled, double-blind trial

OPEN ▲

Diana Apetauerova, MD
Stephanie A. Scala, MA,
CCRP
Robert W. Hamill, MD
David K. Simon, MD,
PhD
Subash Pathak, MS
Robin Ruthazer, MPH
David G. Standaert, MD,
PhD
Talene A. Yacoubian,
MD, PhD

Correspondence to
Dr. Apetauerova:
Diana_apetauerova@lahey.org

ABSTRACT

Objective: An investigator-initiated, multicenter, randomized, placebo-controlled, double-blind clinical trial to determine whether coenzyme Q10 (CoQ10) is safe, well tolerated, and effective in slowing functional decline in progressive supranuclear palsy (PSP).

Methods: Sixty-one participants received CoQ10 (2,400 mg/d) or placebo for up to 12 months. Progressive Supranuclear Palsy Rating Scale (PSPRS), Unified Parkinson's Disease Rating Scale, activities of daily living, Mini-Mental State Examination, the 39-item Parkinson's Disease Questionnaire, and 36-item Short Form Health Survey were monitored at baseline and months 3, 6, 9, and 12. The safety profile of CoQ10 was determined by adverse events, vital signs, and clinical laboratory values. Primary outcome measures were changes in PSPRS and Unified Parkinson's Disease Rating Scale scores from baseline to month 12.

Results: CoQ10 was well tolerated. No statistically significant differences were noted between CoQ10 and placebo groups in primary or secondary outcome measures. A nonsignificant difference toward slower clinical decline in the CoQ10 group was observed in total PSPRS among those participants who completed the trial. Before the final study visit at 12 months, 41% of participants withdrew because of travel distance, lack of perceived benefit, comorbidities, or caregiver issues.

Conclusions: High doses of CoQ10 did not significantly improve PSP symptoms or disease progression. The high withdrawal rate emphasizes the difficulty of conducting clinical trials in patients with PSP.

ClinicalTrials.gov identifier: NCT00382824.

Classification of evidence: This study provides Class II evidence that CoQ10 does not significantly slow functional decline in PSP. The study lacks the precision to exclude a moderate benefit of CoQ10. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e266; doi: 10.1212/NXI.000000000000266

GLOSSARY

ADL = activities of daily living; **CoQ10** = coenzyme Q10; **MMSE** = Mini-Mental State Examination; **PDQ-39** = 39-item Parkinson's Disease Questionnaire; **PSP** = progressive supranuclear palsy; **PSPRS** = Progressive Supranuclear Palsy Rating Scale; **SF-36** = 36-item Short Form Health Survey; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Progressive supranuclear palsy (PSP) is an atypical parkinsonism with tau aggregation and neuron loss.¹ Currently, no therapies treat symptoms or slow the progression of PSP.

Mitochondrial impairment is implicated in PSP^{2,3}; PET studies show decreased glucose metabolism or oxygen utilization in the frontal cortex and striatum in PSP.⁴⁻⁷ Oxidative phosphorylation and mitochondrial enzyme defects have been observed in the brain or muscle of patients with PSP.⁸⁻¹⁰ Cybrids created with mitochondria from patients with PSP confirm mitochondrial dysfunction.¹¹⁻¹³

From the Department of Neurology (D.A., S.A.S.), Lahey Hospital & Medical Center, Burlington, MA; Department of Neurology and Neurobiology (D.G.S., T.A.Y.), University of Alabama Hospital, Birmingham; Department of Neurology (R.W.H.), University of Vermont College of Medicine, Burlington; Department of Neurology (D.K.S.), Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA; and Research Design Center/Biostatistics Research Center (S.P., R.R.), Tufts Clinical & Translational Science Institute, Boston, MA.

Funding information and disclosures are provided at the end of the article. Go to Neurology.org/nn for full disclosure forms. The Article Processing Charge was paid by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Coenzyme Q10 (CoQ10) is a key component of the mitochondrial respiratory chain. CoQ10 reduces toxicity in models of complex I inhibition.^{14–16} A placebo-controlled study in 21 participants with clinically probable PSP showed significant improvement of cerebral energy metabolism and clinical benefits.¹⁷

In the current study, we compared the effect of oral CoQ10 vs placebo in patients with PSP over 12 months. The study design was a prospective, multicenter, randomized, placebo-controlled, double-blind, phase 2 trial of 61 patients with clinically probable PSP. A dosage of 2,400 mg/d was chosen as this is well tolerated and achieves high plasma CoQ10 levels based on CoQ10 studies performed in patients with Parkinson disease. Plasma levels reached a plateau at 2,400 mg/d, suggesting futility of studying higher doses.¹⁸ Prespecified primary outcome measures were changes from baseline in the Progressive Supranuclear Palsy Rating Scale (PSPRS) and the Unified Parkinson's Disease Rating Scale (UPDRS) at 12 months. Secondary outcome measures included change from baseline in the activities of daily living (ADL) score, in intellectual functioning, as measured by the Mini-Mental State Examination (MMSE), and in scales measuring perceived quality of life and health [the 39-item Parkinson's Disease Questionnaire (PDQ-39) and the 36-item Short Form Health Survey (SF-36)] at 12 months.

METHODS **Standard protocol approvals, registrations, and patient consents.** Participants were enrolled between October 2006 and September 2012 at 4 movement disorder clinics in the United States. The study was approved by institutional review boards at participating sites and full written consent was obtained on each participant.

Study design. The clinicaltrials.gov identifier for this investigator-initiated, multicenter, randomized, placebo-controlled, double-blind clinical trial is NCT00382824.

Participants. Eligible participants were aged 40 years and older and fulfilled diagnostic criteria for probable PSP.¹⁹ Participants did not undergo genetic testing and were not classified into subtypes of PSP. Patients receiving antiparkinsonian medications were required to be on stable doses for ≥ 30 days before baseline visit and to maintain medication throughout the study. Antioxidants within 30 days of baseline visit and use of CoQ10 within 60 days of baseline visit were not permissible. Patients were also not allowed to take antioxidants during the study duration. Exclusion criteria included drug-induced parkinsonism; history of pallidotomy, thalamotomy,

deep brain stimulation, or fetal tissue transplant; treatment with methylphenidate hydrochloride, cinnarizine, reserpine, amphetamines, or monoamine oxidase-A inhibitors within 3 months before baseline visit; and pregnancy. Also excluded were patients with a history of active epilepsy, stroke, structural brain disease, electroconvulsive therapy, or known CoQ10 hypersensitivity.

Intervention and clinical evaluation. Informed consent was obtained at the screening visit. Screening procedures included assessment of eligibility criteria, medical history, physical examination, vital signs, weight, height, safety laboratory tests (CBC, basic metabolic profile, liver profile, pregnancy test), CoQ10 level, ECG, and medication review. Participants were evaluated at baseline by PSPRS, UPDRS, ADL, MMSE, PDQ-39, and SF-36 scales.

Each participant was randomly assigned 1:1 using a computerized random number generator by an unblinded research pharmacist to receive CoQ10 at 2,400 mg/d or matching placebo. There was no special randomization for sex, subgroup of PSP, or duration of the disease.

Participants, investigators, and other personnel remained blinded to assignment until study completion. CoQ10 raw material was provided by Kaneka (Pasadena, TX) and wafers were manufactured and provided by Vitaline Formulas (Green Bay, WI) as a chewable wafer containing 300 mg of CoQ10 and 300 IU of vitamin E as a lipophilic carrier. Matching placebo wafers contained 300 IU of vitamin E. At each visit, participants were asked to return the container with any remaining medications. Unused and/or empty containers were collected and the quantity of returned study drug was recorded. Participants could divide the total dose either twice or 4 times daily.

Subsequent visits occurred at months 3, 6, 9, and 12 after randomization. At each visit, vital signs, medication changes, adverse event data, and PSPRS, UPDRS, ADL, MMSE, PDQ-39, and SF-36 scores were obtained. CoQ10 levels and safety laboratory tests were repeated at month 12.

Statistical analysis. The primary research question of the study was to test whether CoQ10 slowed disease progression as measured by the primary outcomes. This study provides Class II evidence to answer this question. Primary efficacy variables were changes in total PSPRS and total UPDRS between baseline and month 12, where change was calculated as the 12-month follow-up score minus the baseline score. Secondary clinical outcome variables included PSP subscales, UPDRS subscales, Schwab and England ADL, MMSE, PDQ-39, and SF-36 scores.

Baseline demographics and UPDRS and PSPRS scores were compared between CoQ10 and placebo groups. Student *t* tests were used to compare continuous variables, with results presented as means and SDs, and χ^2 tests were used to compare distributions of categorical variables. The mean change from baseline to 12-month values for primary and secondary outcomes was compared between CoQ10 and placebo groups using Student *t* tests. The Wilcoxon rank sum test was used to compare the distribution of change in CoQ10 between groups because the SDs between groups were different by a factor of approximately 10; medians and 25th to 75th percentiles are also presented for change in CoQ10. Since the change from baseline to 12-month values was the a priori–defined primary assessment time point, we do not show *p* values comparing CoQ10 and placebo groups at each intermediate follow-up time, although these data are plotted for the primary endpoints together with error bars (mean \pm 2 standard errors).

A scatterplot with a least squares regression line was used to assess the relationship between the change from baseline to 12-month CoQ10 and the change from baseline to 12-month PSPRS. A Pearson correlation coefficient and corresponding p value were computed to describe this relationship.

Characteristics and outcomes of patients who did and did not complete the study were compared using Student t tests and χ^2 tests as described for the comparisons of groups at baseline. To further explore the effect of CoQ10 vs placebo on changes in UPDRS and PSPRS over time, we used pattern mixture models to estimate an adjusted treatment effect including data from participants enrolled but failing to complete the study.²⁰

All analyses were performed using the SAS system for windows (SAS 9.4 TS Level 1M1; SAS Institute Inc., Cary, NC).

RESULTS More than 200 individuals with PSP were approached for inclusion in this trial. Sixty-two patients were consented, examined, and randomized. The primary reason that the remainder of participants were unable to participate was distance to study site. One patient, randomized to CoQ10, was withdrawn soon after enrollment because of initial misdiagnosis and was not included in subsequent analyses. Of the remaining 61 individuals, 31 were assigned to CoQ10 and 30 to placebo (figure 1).

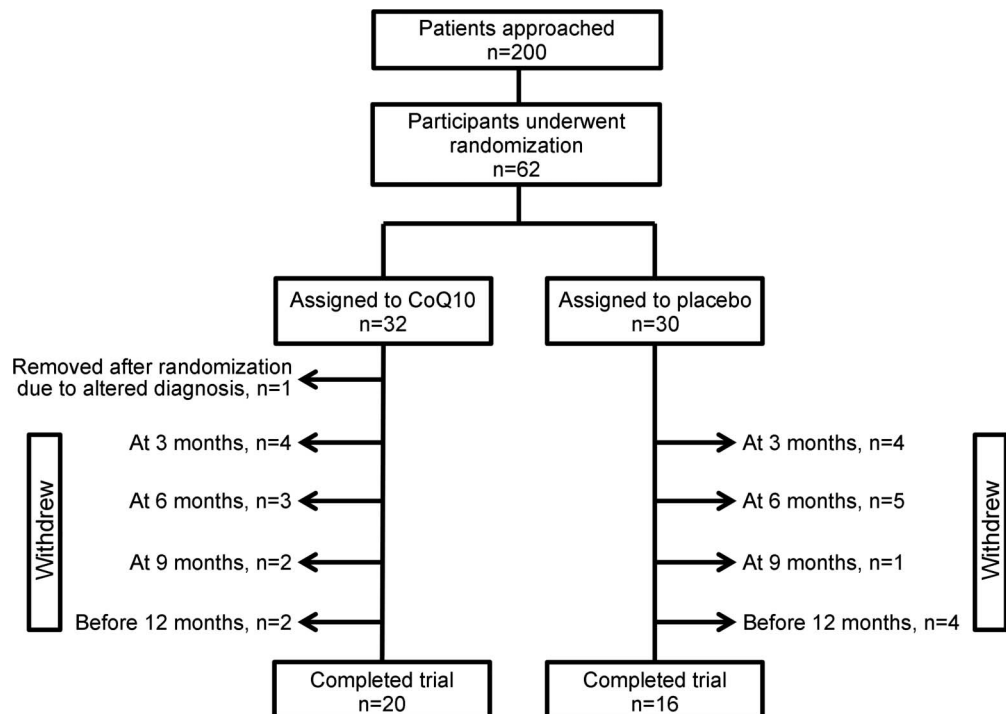
Baseline data. Demographic and baseline clinical characteristics of each group are summarized in table 1. More males were assigned to CoQ10 (74.2% in the CoQ10 group, 46.7% in the placebo group; $p = 0.028$). There were no other significant differences between placebo and treatment groups.

Safety and tolerability. CoQ10 was well tolerated in this study. There were 65 reports of adverse events, most occurring once (table 2). The proportion of participants experiencing adverse events was not statistically different between CoQ10 and placebo groups (48.4% vs 66.7%; $p = 0.15$). Thirteen of these adverse events were considered possibly related, including diarrhea, constipation, gas, nausea, headache, urinary tract infection, diverticulitis, and bleeding ulcer. The proportion of participants with possibly related adverse events was 25.8% in the CoQ10 group and 0% in the placebo group ($p = 0.0028$). All adverse events subsequently resolved. Thirteen serious adverse events (5 in the CoQ10 group and 7 in the placebo group) were reported, and 2 were considered possibly related and included diverticulitis and bleeding ulcer. Serious adverse events included fractures, aspiration pneumonia, benign prostate hypertrophy with obstruction, stent placement, diverticulitis, *Clostridium difficile* infection, bleeding ulcer, and ureteral calculus.

Safety laboratory tests remained stable throughout study. Study drug compliance was recorded at each visit and showed a mean compliance rate of 92%. No patients withdrew because of intolerance or safety issues.

Outcomes and estimation. At each visit, participants were assessed with PSPRS, UPDRS, MMSE, ADL, PDQ-39, and SF-36 scales. Of the initial 61

Figure 1 Participant flowchart



CoQ10 = coenzyme Q10.

Table 1 Comparison of baseline characteristics of randomized patients in the study (n = 61)

	CoQ10 (n = 31)	Placebo (n = 30)	p Value ^a
Sex, male, % (n)	74.2 (23)	46.7 (14)	0.0278
Race, white, % (n)	100.0 (31)	96.7 (29)	0.3054
Age, mean ± SD (n)	65.6 ± 9.5 (31)	67.6 ± 7.8 (30)	0.3679
Never smoked, % (n)	32.3 (10)	46.7 (14)	0.2495
Family Hx PSP, % (n)	0.0 (0)	3.3 (1)	0.3054
Family Hx PD/MD, % (n)	41.9 (13)	23.3 (7)	0.1218
Baseline PSPRS score, mean ± SD (n)	37.6 ± 11.9 (31)	39.6 ± 14.1 (30)	0.5533
Baseline UPDRS score, mean ± SD (n)	45.0 ± 16.1 (31)	51.8 ± 16.6 (30)	0.1118
PD medication use, % (n)	58.1 (18)	56.7 (17)	0.9121

Abbreviations: CoQ10 = coenzyme Q10; Hx = history; MD = movement disorders; PD = Parkinson disease; PSP = progressive supranuclear palsy; PSPRS = Progressive Supranuclear Palsy Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale.

^aThe p values are from t test for age, baseline PSPRS score, and baseline UPDRS score; χ^2 test otherwise.

participants, 36 patients (59%) completed the trial through 12 months.

Primary outcome measures. Mean changes in total PSPRS from baseline to final visit at 12 months for participants who completed the trial were 5.9 ± 10.0 for the CoQ10 group and 11.8 ± 8.6 for the control group. While this suggested slower progression in the CoQ10 group, the difference did not reach

statistical significance ($p = 0.068$; table 3). The change in total PSPRS from baseline at each study visit is shown in figure 2 for all participants, including those who did not complete the full trial. The mean change in the UPDRS total score from baseline to month 12 was not statistically significant (11.5 ± 11.1 for the CoQ10 group and 12.8 ± 9.1 for the placebo group; table 3).

Secondary outcome measures. There were no statistically significant differences in mean changes from baseline to month 12 in ADL, MMSE, PDQ-39, or SF-36 scores between treatment groups (table 3).

CoQ10 serum levels. The CoQ10 group showed a significant increase in serum CoQ10 levels at 12 months (median 3.64 mg/L for CoQ10 group vs 0.05 for placebo group, $p < 0.0001$; table 3). We examined whether change in serum CoQ10 levels correlated with change in total PSPRS at 12 months. The degree of increase in serum CoQ10 in patients who completed the study was weakly associated with less decline in PSPRS score at 12 months ($r = -0.363$; $p = 0.06$).

Withdrawal rate. In the CoQ10 group, 20 of 31 participants completed the study through 12 months. Among the control group, 16 of 30 participants completed the study. In both groups, participants withdrew throughout the study course, and not at any

Table 2 Adverse events (n = 61)

Patient level comparisons	CoQ10 (n = 31)	Placebo (n = 30)	p Value ^a
Patients with ≥ 1 AE	48.4 (15)	66.7 (20)	0.1489
Patients with ≥ 1 SAE	16.1 (5)	23.3 (7)	0.4792
Patients with ≥ 1 possibly related AE	25.8 (8)	0.0 (0)	0.0028
Patients with ≥ 1 related SAE	6.5 (2)	0.0 (0)	0.1572
	No. of events in CoQ10 patients	No. of events in placebo patients	Total no. of events
Event count data			
Total no. of AEs	27	38	65
Total no. of SAEs	5	8	13
Total no. of related AEs	13	0	13
Total no. of serious and related AEs	2	0	2
Type of event (in at least 2 study participants)			
UTI	4	1	5
Constipation	1	3	4
Cataract	2	1	3
Nausea	2	1	3
Diarrhea	2	0	2
Dizziness	0	2	2

Abbreviations: AE adverse event; CoQ10 = coenzyme Q10; SAE = serious adverse event; UTI = urinary tract infection. Data represent % (n) or n.

^aThe p values are from χ^2 test.

Table 3 Comparison of primary and secondary outcomes of participants who completed the visit at 12 months (n = 36)

	CoQ10 (n = 20)	Placebo (n = 16)	p Value
Primary outcomes: Change from baseline to 12 mo total scores			
Change in PSPRS at 12 mo	5.9 ± 10.0 (20)	11.8 ± 8.6 (16)	0.0675
Change in UPDRS at 12 mo	11.5 ± 11.1 (20)	12.8 ± 9.1 (16)	0.6957
Secondary outcomes: 12 mo minus baseline			
ΔPSPRS subscore I at 12 mo	1.8 ± 3.4 (20)	1.9 ± 3.4 (16)	0.9138
ΔPSPRS subscore II at 12 mo	-0.0 ± 2.4 (20)	0.3 ± 2.4 (16)	0.7159
ΔPSPRS subscore III at 12 mo	0.9 ± 1.2 (20)	1.1 ± 1.2 (16)	0.6029
ΔPSPRS subscore IV at 12 mo	1.2 ± 2.9 (20)	2.5 ± 1.8 (16)	0.1134
ΔPSPRS subscore V at 12 mo	0.9 ± 2.0 (20)	1.4 ± 1.9 (16)	0.4798
ΔPSPRS subscore VI at 12 mo	2.3 ± 2.6 (20)	4.0 ± 3.0 (16)	0.0779
ΔUPDRS subscore I at 12 mo	-0.4 ± 2.3 (20)	-0.1 ± 1.5 (16)	0.7397
ΔUPDRS subscore II at 12 mo	4.1 ± 5.6 (20)	5.8 ± 5.4 (16)	0.3629
ΔUPDRS subscore III at 12 mo	7.5 ± 5.1 (20)	7.3 ± 5.6 (16)	0.9117
ΔUPDRS subscore IV at 12 mo	0.4 ± 0.7 (20)	0.0 ± 0.8 (16)	0.1668
ΔADL score at 12 mo	-13.5 ± 20.6 (20)	-18.4 ± 15.9 (16)	0.4357
ΔMMSE score at 12 mo	-1.3 ± 3.4 (20)	-1.3 ± 1.8 (15)	0.9864
ΔPDQ score at 12 mo	3.4 ± 13.9 (20)	7.5 ± 12.6 (16)	0.3755
ΔSF-36 score at 12 mo	-2.1 ± 19.1 (20)	-7.2 ± 15.4 (16)	0.3846
Δ in CoQ10 at 12 mo, n	16	12	
Mean ± SD, mg/L	4.01 ± 2.43	0.07 ± 0.27	<0.0001
Median (25th to 75th percentile)	3.64 (2.59 to 6.25)	0.05 (-0.1 to 0.15)	<0.0001

Abbreviations: ADL = activities of daily living; CoQ10 = coenzyme Q10; MMSE = Mini-Mental State Examination; PDQ = Parkinson's Disease Questionnaire; PSPRS = Progressive Supranuclear Palsy Rating Scale; SF-36 = 36-item Short Form Health Survey; UPDRS = Unified Parkinson's Disease Rating Scale.

Data represent mean ± SD (n) unless otherwise indicated.

one particular time. Withdrawal rates were similar among different study sites. Main withdrawal reasons stated by participants were travel distance, lack of perceived benefit, comorbidities, or caregiver issues.

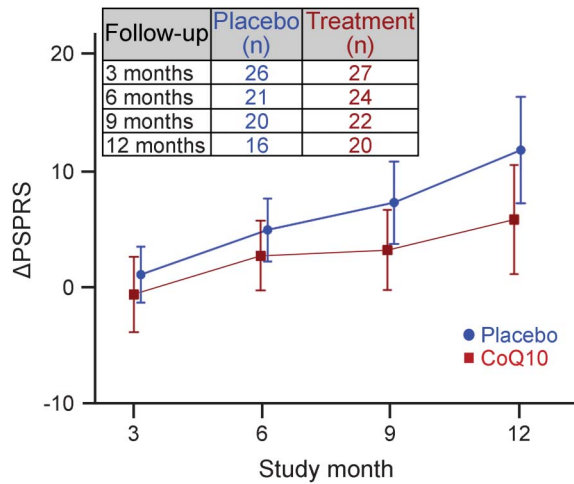
Because of concern that the high withdrawal rate may have introduced bias, we compared baseline demographic and clinical characteristics between those in the CoQ10 group who completed the study and those in the placebo group who completed the study. There were no statistically significant differences except for sex ($p = 0.0091$), which was also noted in the total cohort (table 1).

We also compared demographic and clinical characteristics of those who completed the trial and those who withdrew (table 4). While baseline characteristics did not differ, there was a significant difference in the change in the total PSPRS between those who withdrew and those who did not. Those who completed the trial showed less clinical decline as measured by total PSPRS compared to those who withdrew before 12 months. This suggests that those declining more quickly were more likely to withdraw.

We then stratified by treatment the comparison between those who withdrew and those who did not (table 4). Participants treated with CoQ10 who completed the trial showed less decline in the total PSPRS at 3 months (-2.4 ± 8.1) compared to those who withdrew before 12 months (4.6 ± 6.2 ; $p = 0.05$). Results for the UPDRS were similar. In contrast, in the control group, those who withdrew did not significantly differ from those who completed the study regarding change in total PSPRS or UPDRS scores, although the average declines were higher among participants who withdrew.

Because of the high dropout rate and the concern that withdrawals were not necessarily random, we reanalyzed the primary outcome data using data from the whole cohort. We used pattern mixture model analysis to adjust for missing data points for those patients who withdrew before the final visit. We adjusted for baseline PSPRS or UPDRS scores and sex. Based on this analysis, there was no treatment difference for either total PSPRS or UPDRS scores.

Figure 2 Change in total PSPRS score from baseline to each study visit for all participants



The change in total PSPRS score is calculated as the change from baseline to each visit. The mean value and 95% confidence interval are plotted at each visit for all participants who completed that particular visit. CoQ10 = coenzyme Q10; PSPRS = Progressive Supranuclear Palsy Rating Scale.

DISCUSSION This study demonstrates that 12 months of treatment in patients with PSP with 2,400 mg of CoQ10 daily is safe and tolerable. Sixty-one participants received 2,400 mg/d or placebo for up to 12 months. Compliance rates were high, approximately 92%. Those taking CoQ10 showed less clinical decline in total PSPRS score among those who completed the study, but the difference was not statistically significant. No statistically significant differences were noted between CoQ10 and placebo groups in other clinical assessments.

Limitations of our study design include small sample size and short follow-up period. A total of 61 participants were enrolled in the study. With an even smaller sample size remaining at 12 months, this study does not have sufficient power to identify a modest therapeutic benefit of CoQ10. The separation between placebo and CoQ10 groups in PSPRS appears more prominent over time (figure 2), suggesting that a greater difference might have been noted with longer follow-up. Another issue is that most participants were fairly advanced in disease at the onset of the study, partly because many years of illness often pass before a clear clinical diagnosis of PSP can be made. Intervention with CoQ10 at an earlier stage of disease may be more effective.

An unanticipated limitation of our study was the high withdrawal rate. This does not appear related to the treatment; rather, it reflects the difficulty of maintaining continued study participation of a cohort of patients with this debilitating disease. The main stated reasons for withdrawal included lack of perceived benefit and travel distance. We compared the demographics of placebo and

CoQ10 groups among those who completed the group and saw statistically significant differences in sex only, as with the whole cohort. We also compared demographic and clinical data between those participants who withdrew early and those who completed the trial, and saw that those who withdrew showed a greater rate of decline in total PSPRS, suggesting that those who progressed faster were more likely to withdraw early. To account for the dropout rate, we reanalyzed all patients regardless of withdrawal using pattern mixture model analysis. By this analysis, there was no significant difference in total PSPRS or UPDRS between groups.

Comparing the CoQ10 group that completed the study to the CoQ10 group that withdrew early, we saw a difference in the progression rate as assessed by change in total PSPRS score at 3 months. The average total PSPRS score declined more rapidly among those in the treatment group who withdrew before 12 months. This raises the concern that the treatment effect we saw among those who completed the trial is skewed by the fact that the patients who withdrew are progressing more quickly. Alternatively, there may be a subgroup among the CoQ10-treated patients that particularly respond to CoQ10, and, as a result, were more likely to continue the study. One possibility is that different clinical subtypes of PSP may respond differentially to CoQ10. Thus, it remains possible that there is a subgroup of patients with PSP in which CoQ10 is a beneficial treatment.

The high withdrawal rate in this study over the 12-month study period reinforces the fact that clinical trials in PSP are difficult to perform. Because of the difficulty in making the diagnosis of PSP, especially by non-movement disorder specialists, patients are often advanced by the time they are diagnosed with PSP. Patients also are usually advanced in the disease process by the time they meet diagnostic criteria for probable PSP,¹⁹ the criteria we used for inclusion in the study. As mobility of the participants becomes more restricted over time, the ability of patients to return for follow-up study visits declines. Indeed, we found that those participants who were declining more rapidly as measured by the change in PSPRS were more likely to drop out of the study. Because of this challenge of maintaining study participation of patients with PSP, the ideal of a longer period of observation beyond 1 year may not be feasible for a fair number of patients with PSP.

A smaller study evaluated CoQ10 treatment for 6 weeks in 21 patients.¹⁷ A small but statistically significant improvement was observed in PSPRS and the Frontal Assessment Battery in CoQ10-treated participants. Similar to our study, no significant differences were observed in UPDRS, MMSE, and ADL scores. Trial differences include length of treatment and the CoQ10 dose and formulation. In the 21-patient

Table 4 Comparison of baseline characteristics and outcomes between participants who completed the study and those who withdrew before the final visit

	Completed study (n = 36)	Withdrew before final visit (n = 25)	p Value
Baseline characteristics and changes over time (n = 61, all participants)			
Sex, male	66.7 (24/36)	52.0 (13/25)	0.2488
Race, white	97.2 (35/36)	100.0 (25/25)	0.4008
Age	65.9 ± 8.5 (36)	67.5 ± 9.1 (25)	0.5012
Never smoked	36.1 (13/36)	44.0 (11/25)	0.5351
Family Hx PSP	2.8 (1/36)	0.0 (0/25)	0.4008
Family Hx PD/MD	33.3 (12/36)	32.0 (8/25)	0.9131
Baseline PSPRS score	37.5 ± 11.6 (36)	40.3 ± 14.7 (25)	0.4095
Baseline UPDRS score	46.4 ± 15.1 (36)	51.2 ± 18.5 (25)	0.2757
PD medication use	66.7 (24/36)	44.0 (11/25)	0.0783
Change in UPDRS score			
3 mo	1.0 ± 5.4 (36)	4.5 ± 7.9 (17)	0.0625
6 mo	5.5 ± 5.9 (34)	10.2 ± 11.2 (11)	0.0785
9 mo	7.0 ± 6.2 (36)	15.2 ± 10.7 (6)	0.0109
Change in PSPRS score			
3 mo	-1.1 ± 7.5 (36)	3.1 ± 5.5 (17)	0.0478
6 mo	2.6 ± 6.4 (34)	7.3 ± 6.1 (11)	0.0421
9 mo	4.2 ± 7.5 (36)	11.2 ± 7.7 (6)	0.0419
Randomized to treatment group	55.6 (20/36)	44.0 (11/25)	0.3746
Baseline characteristics and changes over time (n = 31, CoQ10-treated)			
Sex, male	85.0 (17/20)	54.5 (6/11)	0.0637
Race, white, %	100	100	
Age	65.8 ± 10.0 (20)	65.3 ± 9.0 (11)	0.8959
Never smoked	30.0 (6/20)	36.4 (4/11)	0.7169
Family Hx PSP	0	0	
Family Hx PD/MD	40.0 (8/20)	45.5 (5/11)	0.7684
Baseline PSPRS score	38.5 ± 10.9 (20)	36.2 ± 14.0 (11)	0.6193
Baseline UPDRS score	44.9 ± 13.9 (20)	45.3 ± 20.3 (11)	0.9522
PD medication use	60.0 (12/20)	54.5 (6/11)	0.7684
Change in UPDRS score			
3 mo	0.1 ± 3.5 (20)	4.0 ± 5.9 (7)	0.0426
6 mo	5.5 ± 5.0 (20)	7.8 ± 10.3 (4)	0.5017
9 mo	6.7 ± 6.7 (20)	14.0 ± 7.1 (2)	0.1557
Change in PSPRS score			
3 mo	-2.4 ± 8.1 (20)	4.6 ± 6.2 (7)	0.0499
6 mo	1.6 ± 6.9 (20)	8.5 ± 5.3 (4)	0.0750
9 mo	2.4 ± 7.5 (20)	11.5 ± 6.4 (2)	0.1163
Baseline characteristics and changes over time (n = 30, control)			
Sex, male	43.8 (7/16)	50.0 (7/14)	0.7321
Race, white	93.8 (15/16)	100.0 (14/14)	0.3414
Age	66.2 ± 6.4 (16)	69.2 ± 9.1 (14)	0.2968
Never smoked	43.8 (7/16)	50.0 (7/14)	0.7321

Continued

Table 4 Continued

	Completed study (n = 36)	Withdrew before final visit (n = 25)	p Value
Family Hx PSP	6.3 (1/16)	0.0 (0/14)	0.3414
Baseline PSPRS score	25.0 (4/16)	21.4 (3/14)	0.8175
Baseline UPDRS score	36.3 ± 12.8 (16)	43.5 ± 15.0 (14)	0.1638
PD medication use	75.0 (12/16)	35.7 (5/14)	0.0303
Change in UPDRS score			
3 mo	2.2 ± 7.1 (16)	4.9 ± 9.3 (10)	0.4085
6 mo	5.5 ± 7.3 (14)	11.6 ± 12.2 (7)	0.1665
9 mo	7.4 ± 5.8 (16)	15.8 ± 13.1 (4)	0.0629
Change in PSPRS score			
3 mo	0.6 ± 6.5 (16)	2.0 ± 5.1 (10)	0.5587
6 mo	4.1 ± 5.5 (14)	6.6 ± 6.9 (7)	0.3913
9 mo	6.4 ± 7.2 (16)	11.0 ± 9.2 (4)	0.2871

Abbreviations: CoQ10 = coenzyme Q10; Hx = history; MD = movement disorders; PD = Parkinson disease; PSP = progressive supranuclear palsy; PSPRS = Progressive Supranuclear Palsy Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale.

study,¹⁷ participants were followed for 6 weeks, while participants were followed for 1 year in our study. This raises the possibility that CoQ10 could have a transient but unsustained benefit. In our study, all participants were treated with 2,400 mg daily compared to a dose of 5 mg/kg body weight in the smaller study. Differences in CoQ10 formulations could also account for differences in studies. Average serum CoQ10 levels were higher for the above-mentioned 21-patient study compared to our study; thus, serum CoQ10 level differences could account for the different results between these studies.

CoQ10 at 2,400 mg daily is safe and well tolerated in patients with PSP. No statistically significant benefits were observed, although a nonsignificant, slower clinical decline in the CoQ10 group was seen in the PSPRS score among those who completed the study. These data suggest that any benefit of CoQ10 in PSP is modest at best, and that demonstrating this benefit would require a much larger trial with longer duration. Such a trial would also need to address the difficulties of maintaining continued trial participation over a long duration in this patient population.

AUTHOR CONTRIBUTIONS

D.A. contributed to study concept and design, data acquisition, data interpretation, and drafting and revision of the manuscript. S.A.S. contributed to study design, data acquisition, study coordination, and drafting the manuscript. R.W.H., D.K.S., and D.G.S. contributed to data acquisition, data interpretation, and critical revision of the manuscript. S.P. and R.R. contributed to data analysis and interpretation. T.A.Y. contributed to data acquisition, data interpretation, and drafting and revision of the manuscript.

ACKNOWLEDGMENT

The authors thank Kaneka for providing raw CoQ10 and Vitaline Formulas for manufacturing the CoQ10 and placebo materials for the study duration. A special thank you to site research staff at Lahey Hospital & Medical

Center, Burlington, MA: Sharon Lamont; University of Alabama Hospital, Birmingham: Molly Moran, Jennifer Newsome, RN, CCRC, and Jenna T. Smith, RN, BSN; University of Vermont College, Burlington: Marilee C. Jones, MAMC, and Shannon R. Lenox; Beth Israel Deaconess Medical Center, Boston, MA: Shannon Donovan, Lauren Kraics, Chen Lim, Jared Miller, Peggy Rose, BSN, RN, Althea Silver, MPH, BSN, RN, and Adam Simmons.

STUDY FUNDING

This study was supported by a grant from the Society for PSP and the Robert E. Wise Research and Education Institute. The CoQ10 and matching placebo were formulated and packaged with minimal cost by Vitaline Formulas and Kaneka.

DISCLOSURE

D. Apetauerova has consulted for Highland Instruments Inc., receives research support from PSP. S.A. Scala reports no disclosures. R.W. Hamill is on the editorial board for *Neurotherapeutics*, received research support from the Michael J. Fox Foundation. D.K. Simon serves on the scientific advisory board for the Weston Brain Institute, is on the editorial board for *Annals of Neurology*, has consulted for Lysosomal Therapeutics, Inc., received research support from Lysosomal Therapeutics, Edison Pharmaceuticals, NIH/NINDS, Weston Brain Institute. S. Pathak reports no disclosures. R. Ruthazer received research support from NIH/NINDS. D.G. Standaert served on the scientific advisory board for Shire/ViroPharma, American Parkinson Disease Association, received honoraria from the Movement Disorder Society, Georgia Regents University, is an associate editor for *Movement Disorders*, receives publishing royalties from McGraw-Hill, has consulted for Serina Therapeutics, Kirchner Group, Teva Neuroscience, AbbVie, US Attorney's Office, performed grant reviews for the Michael J. Fox Foundation, NIH, American Institute of Biological Sciences, received research support from AbbVie, Acerta Pharma, Ceregene (Sangamo) Quintiles, NIH, Alabama Department of Commerce, American Parkinson Disease Association, Michael J. Fox Foundation for Parkinson Research, Bachmann-Strauss Dystonia & Parkinson Foundation, Dystonia Medical Research Foundation. T.A. Yacoubian received travel funding and/or speaker honoraria from the Movement Disorders Society, NIH, Michael J. Fox Foundation, holds a patent on the use of 14-3-3s in neurodegeneration, received research support from NINDS, University of Alabama at Birmingham, AL Drug Discovery Alliance, American Parkinson Disease Association, Michael J. Fox Foundation, Parkinson Association of Alabama, Alzheimer's of Central Alabama. Go to Neurology.org/nn for full disclosure forms.

Received December 10, 2015. Accepted in final form June 15, 2016.

REFERENCES

1. Dickson DW, Ahmed Z, Algom AA, Tsuboi Y, Josephs KA. Neuropathology of variants of progressive supranuclear palsy. *Curr Opin Neurol* 2010;23:394–400.
2. Albers DS, Beal MF. Mitochondrial dysfunction in progressive supranuclear palsy. *Neurochem Int* 2002;40:559–564.
3. Ries V, Oertel WH, Hoglinger GU. Mitochondrial dysfunction as a therapeutic target in progressive supranuclear palsy. *J Mol Neurosci* 2011;45:684–689.
4. Blin J, Baron JC, Dubois B, et al. Positron emission tomography study in progressive supranuclear palsy: brain hypometabolic pattern and clinicometabolic correlations. *Arch Neurol* 1990;47:747–752.
5. D'Antona R, Baron JC, Samson Y, et al. Subcortical dementia: frontal cortex hypometabolism detected by positron tomography in patients with progressive supranuclear palsy. *Brain* 1985;108:785–799.
6. Foster NL, Gilman S, Berent S, Morin EM, Brown MB, Koeppe RA. Cerebral hypometabolism in progressive supranuclear palsy studied with positron emission tomography. *Ann Neurol* 1988;24:399–406.
7. Leenders KL, Frackowiak RS, Lees AJ. Steele-Richardson-Olszewski syndrome: brain energy metabolism, blood flow and fluorodopa uptake measured by positron emission tomography. *Brain* 1988;111:615–630.
8. Albers DS, Augood SJ, Park LC, et al. Frontal lobe dysfunction in progressive supranuclear palsy: evidence for oxidative stress and mitochondrial impairment. *J Neurochem* 2000;74:878–881.
9. Di Monte DA, Harati Y, Jankovic J, Sandy MS, Jewell SA, Langston JW. Muscle mitochondrial ATP production in progressive supranuclear palsy. *J Neurochem* 1994;62:1631–1634.
10. Martinelli P, Scaglione C, Lodi R, Iotti S, Barbiroli B. Deficit of brain and skeletal muscle bioenergetics in progressive supranuclear palsy shown in vivo by phosphorus magnetic resonance spectroscopy. *Mov Disord* 2000;15:889–893.
11. Albers DS, Augood SJ, Martin DM, Standaert DG, Vonsattel JP, Beal MF. Evidence for oxidative stress in the subthalamic nucleus in progressive supranuclear palsy. *J Neurochem* 1999;73:881–884.
12. Chirichigno JW, Manfredi G, Beal MF, Albers DS. Stress-induced mitochondrial depolarization and oxidative damage in PSP cybrids. *Brain Res* 2002;951:31–35.
13. Swerdlow RH, Golbe LI, Parks JK, et al. Mitochondrial dysfunction in cybrid lines expressing mitochondrial genes from patients with progressive supranuclear palsy. *J Neurochem* 2000;75:1681–1684.
14. Abidin AA, Hamouda HE. Mechanism of the neuroprotective role of coenzyme Q10 with or without L-dopa in rotenone-induced parkinsonism. *Neuropharmacology* 2008;55:1340–1346.
15. Beal MF, Matthews RT, Tieleman A, Shults CW. Coenzyme Q10 attenuates the 1-methyl-4-phenyl-1,2,3, tetrahydropyridine (MPTP) induced loss of striatal dopamine and dopaminergic axons in aged mice. *Brain Res* 1998;783:109–114.
16. Moon Y, Lee KH, Park JH, Geum D, Kim K. Mitochondrial membrane depolarization and the selective death of dopaminergic neurons by rotenone: protective effect of coenzyme Q10. *J Neurochem* 2005;93:1199–1208.
17. Stamelou M, Reuss A, Pilatus U, et al. Short-term effects of coenzyme Q10 in progressive supranuclear palsy: a randomized, placebo-controlled trial. *Mov Disord* 2008;23:942–949.
18. Shults CW, Flint Beal M, Song D, Fontaine D. Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. *Exp Neurol* 2004;188:491–494.
19. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology* 1996;47:1–9.
20. Hedeker D, Gibbons RD. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychol Methods* 1997;2:64–78.