

A randomized, placebo-controlled trial of coenzyme Q₁₀ and remacemide in Huntington's disease

The Huntington Study Group*

Article abstract—*Objectives:* To determine whether chronic treatment with coenzyme Q₁₀ or remacemide hydrochloride slows the functional decline of early Huntington's disease (HD). *Methods:* The authors conducted a multicenter, parallel group, double-blind, 2 × 2 factorial, randomized clinical trial. Research participants with early HD (n = 347) were randomized to receive coenzyme Q₁₀ 300 mg twice daily, remacemide hydrochloride 200 mg three times daily, both, or neither treatment, and were evaluated every 4 to 5 months for a total of 30 months on assigned treatment. The prespecified primary measure of efficacy was the change in total functional capacity (TFC) between baseline and 30 months. Safety measures included the frequency of clinical adverse events. *Results:* Neither intervention significantly altered the decline in TFC. Patients treated with coenzyme Q₁₀ showed a trend toward slowing in TFC decline (13%) over 30 months (2.40- versus 2.74-point decline, *p* = 0.15), as well as beneficial trends in some secondary measures. There was increased frequency of nausea, vomiting, and dizziness with remacemide and increased frequency of stomach upset with coenzyme Q₁₀. *Conclusions:* Neither remacemide nor coenzyme Q₁₀, at the dosages studied, produced significant slowing in functional decline in early HD.

NEUROLOGY 2001;57:397-404

Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative disorder characterized by selective degeneration of striatal spiny neurons and is caused by a CAG trinucleotide repeat expansion in the *huntingtin* gene. Clinical features include movement disorders, principally chorea and dystonia, cognitive decline, and a spectrum of behavioral disorders. Clinical manifestations begin typically in the fourth decade and are characterized by inexorable, progressive deterioration in functional capacity and independence. Toxin and transgenic animal models of HD implicate deficits in energy metabolism, oxidative damage, and glutamatergic N-methyl D-aspartate (NMDA)-mediated receptor activation.¹⁻⁵ Based on these data, we conducted a controlled clinical trial to assess the impact of coenzyme Q₁₀, an antioxidant and cofactor involved in mitochondrial electron transfer, and remacemide hydrochloride, a noncompetitive NMDA receptor antagonist. Results

of pilot clinical trials in patients with HD suggested that both coenzyme Q₁₀ and remacemide were well tolerated at the dosages to be studied.⁶⁻⁷

Methods. *Enrollment.* A total of 347 eligible participants were enrolled at 23 sites between July 1997 and June 1998. This study was reviewed and approved by the institutional review board at each participating site. All research participants gave written informed consent. An independent safety monitoring committee periodically reviewed the safety data.

Entry criteria. Eligible participants were individuals who had HD with an appropriate family history or a confirmatory CAG expansion, and were in Stages I or II of illness with a total functional capacity (TFC) of 7 or more units.⁸ These individuals were ambulatory and largely independent in daily activities. Patients were excluded if they had taken coenzyme Q₁₀ in the preceding 3 months or if they had unstable medical or psychiatric illness.

Study design. A randomized, double-blind, placebo-controlled, parallel-group, 2 × 2 factorial design was used. The four treatment groups were remacemide hydrochloride (AstraZeneca, Wayne, PA), coenzyme Q₁₀ (Vitaline, Ashland, OR), a combination of both active treatments, or

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the August 14 issue to find title link for this article.

See also pages 375 and 515

*See the Appendix on page 403 for a complete listing of the members of the Huntington Study Group.

Supported primarily by NIH, NINDS (#NS R01-35284), and also by General Clinical Research Centers (grants RR00645, RR00042, RR00044, RR01066, RR07122), AstraZeneca, and Vitaline.

Received May 1, 2001. Accepted in final form May 24, 2001.

Address correspondence and reprint requests to Dr. Karl Kieburtz, University of Rochester Medical Center, 1351 Mt. Hope Avenue, Suite 220, Rochester, NY 14620.

matching placebo for both treatments. The computer-generated randomization plan was stratified by investigator.

Study visits. At an initial screening visit participants signed a consent statement, had their complete medical history reviewed, and underwent a physical examination and laboratory tests. At the baseline visit participants were evaluated using the Unified Huntington's Disease Rating Scale (UHDRS), a standardized and reliable instrument used in clinical trials for assessing the severity of clinical features of HD.⁹ The UHDRS includes assessment of functional capacity, motor and behavioral features, and cognitive performance. The TFC scale ranges from 13 (normal) to 0 (total care) and assesses capacity to work, handle finances, perform domestic chores and self-care tasks, and live independently. The other UHDRS measures of function also decrease with worsening disability. For the UHDRS measures of motor and behavior, zero indicates normal function and increasing scores reflect worsening function. The UHDRS cognitive scores decrease with worsening cognitive performance. Supplemental neuropsychologic testing performed included the Hopkins Verbal Learning Test,¹⁰ the Brief Test of Attention,¹¹ the Trail-making Test, a test of visuomotor speed,¹² and the Conditional Associative Learning Test, a test of nonverbal learning.¹³ Investigators were trained on the use of all scales prior to starting the trial. At the baseline visit, participants were randomized to experimental treatments and then reevaluated at 1, 4, 8, 12, 16, 20, 25, and 30 months thereafter. At each visit UHDRS ratings, vital signs, and reports of concomitant medications and adverse events were obtained. Safety laboratory tests were assessed at baseline and then at 1, 8, 20, and 30 months. Blood levels of coenzyme Q₁₀ and remacemide were assessed at baseline and then at 8 and 30 months; however, the results are not yet available.

Study intervention. Research participants took coenzyme Q₁₀ 300 mg chewable wafers or matching placebo orally with food twice daily approximately 12 hours apart, and remacemide hydrochloride 200 mg tablets or matching placebo orally three times daily approximately 8 hours apart, throughout the 30-month duration of the study. In the event of clinical intolerability, participants were permitted to reduce the dosage of experimental medications to one wafer of coenzyme Q₁₀ or placebo daily and one tablet of remacemide 200 mg or placebo twice daily. In the event of clinical intolerability that precluded the continued administration of the experimental intervention, participants were withdrawn prematurely from experimental medications but otherwise participated in all study evaluations, if willing.

Outcome variables. The prespecified primary measure of efficacy was the change in TFC between baseline and 30 months. Other outcomes prespecified in the analysis plan as efficacy variables of particular interest were the total UHDRS motor score, Stroop Test, Independence Scale, Hopkins Verbal Learning Test, Brief Test of Attention, and Conditional Associative Learning Test. Other secondary efficacy outcome variables included changes on the UHDRS subscales (motor, behavioral, cognitive, functional) and the supplemental neuropsychologic tests. Measures of safety included the frequency and severity of individual adverse experiences and abnormal labora-

tory test or ECG results, as well as changes from baseline to 30 months in laboratory test results and vital signs.

Statistical analysis. Sample size. The planned enrollment in this study was 340 participants. Data from a previous clinical trial in HD¹⁴ suggested that individuals with a baseline TFC greater than or equal to 7 would have an average decline in TFC of 1.25 \pm 1.49 units over a 30-month period. In addition to this, we made the assumption that there would be no statistical interaction between coenzyme Q₁₀ and remacemide based on existing evidence that these agents act by different but complementary pharmacologic mechanisms. Therefore, the sample size was chosen to provide adequate power to detect main effects of coenzyme Q₁₀ and remacemide. A sample size of 296 subjects (74 in each of the four treatment combinations) was chosen to provide >80% power to detect a 40% attenuation of TFC decline (absolute difference of 0.50 TFC units) in subjects receiving coenzyme Q₁₀ (n = 148) compared with subjects not receiving coenzyme Q₁₀ (n = 148), using a two-tailed *t*-test at the 5% level of significance. These calculations apply also to detection of differences between the remacemide and no-remacemide groups. The planned sample size was increased to 340 subjects to account for an anticipated 15% rate of subject withdrawal.

Statistical analysis. Analysis of the primary outcome variable used an analysis of covariance model with coenzyme Q₁₀ treatment and remacemide treatment as the factors of interest, center as a stratification factor, and baseline TFC score as a covariate. Two-tailed *t*-tests for the main effects of coenzyme Q₁₀ and remacemide were performed, and 95% confidence intervals were computed for these effects. The assumption of no statistical interaction between coenzyme Q₁₀ and remacemide was examined by adding the appropriate interaction term to the above model and testing for its significance. Interactions between treatment and center were explored in a similar fashion. The above analyses were repeated for the secondary outcome variables for efficacy, as well as for laboratory test results and vital signs. Fisher's exact tests were used to compare treatment groups with regard to occurrences of adverse events.

The primary statistical analyses were performed according to the intention-to-treat principle. For the analyses of the outcome variables for efficacy, if a subject was missing a response at a particular visit, the last observation for that subject was carried forward and imputed for that visit. The analyses were repeated using other strategies for imputation, and again using only available data (i.e., without imputation). Data from subjects who discontinued treatment but agreed to be followed were included in all analyses. Unless otherwise noted, the analyses reported are those based on changes from baseline to the last observed value. Because of the low rates of subject withdrawal, results of other analyses were not substantively different than those reported.

Results. Comparability of groups at baseline. The four treatment groups were comparable at baseline with regard to demographic and clinical variables (table 1). There was parity of gender distribution, and 95% of the participants were Caucasian. The average age at entry was 47.9 \pm 10.5 (mean \pm SD) years. Participants had been symptomatic for

Table 1 Subject characteristics at baseline

Variable	Placebo, n = 87	Coenzyme Q ₁₀ , n = 87	Remacemide, n = 86	Combination, n = 87
Age	48.6 (10.4)	47.5 (10.1)	47.4 (11.0)	48.2 (10.7)
Male gender, %	44.8	54.0	60.5	43.7
Caucasian, %	92.0	93.1	96.5	98.9
Education, y	14.3 (3.1)	14.4 (3.3)	14.2 (2.6)	13.5 (2.6)
Years since symptom onset	4.7 (3.7)	5.3 (2.7)	4.9 (2.6)	4.6 (3.2)
Years since diagnosis	2.3 (2.0)	3.3 (2.3)	2.6 (2.2)	2.3 (2.0)
CAG repeat length	44.6 (4.8)	45.3 (4.6)	45.6 (4.5)	44.4 (3.6)
Mode of inheritance, %				
Mother	44.8	47.1	47.7	46.0
Father	46.0	49.4	38.4	42.5
Unknown	9.2	3.4	14.0	11.5

Values are mean (SD) unless otherwise indicated.

4.9 ± 3.0 years and were diagnosed with HD for approximately 2.6 ± 2.1 years. The average CAG trinucleotide repeat length was 44.8 ± 5.1. There was a similar distribution of maternal or paternal inheritance. Distributions of the baseline values of primary and secondary outcome variables are summarized in table 2 (additional data available online at www.neurology.org). The average TFC score was 10.2 ± 1.8, and the mean UHDRS motor score was 31.1 ± 14.0, reflecting mild to moderate disease severity.

Tolerability of interventions. The flow of participants is illustrated in figure 1. There were no significant differ-

ences among treatment groups regarding the proportion of participants who completed the study on their assigned treatments, although the proportions were lower among participants treated with remacemide.

Thirty-eight participants withdrew prior to the planned completion of the trial (figure 1). Most participant withdrawals in the placebo and coenzyme Q₁₀ groups were not related to adverse events; however, many of the withdrawals in the remacemide and combined treatment group were due to adverse experiences (n = 11), principally psychiatric disturbances (n = 6) including depression and agitation. A

Table 2 Outcome variables: baseline values

Variable	Placebo, n = 87	Coenzyme Q ₁₀ , n = 87	Remacemide, n = 86	Combination, n = 87
Primary outcome				
Total functional capacity	10.3 (1.7)	10.1 (1.8)	10.0 (2.0)	10.3 (1.9)
Secondary outcomes				
UHDRS functional				
Functional assessment	22.5 (1.8)	22.0 (2.6)	22.0 (2.8)	22.2 (2.7)
Independence scale	87.4 (8.8)	86.8 (9.2)	85.4 (9.7)	87.1 (10.0)
UHDRS motor				
Total	31.0 (13.4)	31.8 (13.4)	32.0 (14.9)	29.4 (14.5)
Maximal chorea	9.1 (4.4)	9.0 (4.2)	9.3 (4.3)	9.3 (4.7)
UHDRS cognitive				
Verbal fluency	23.5 (10.9)	24.9 (11.6)	25.0 (11.2)	24.6 (12.2)
Symbol digit	24.4 (8.5)	27.0 (10.9)	25.9 (9.9)	28.0 (12.2)
Stroop color naming	47.7 (12.6)	50.4 (17.9)	49.3 (15.0)	50.1 (17.0)
Stroop word reading	61.6 (18.0)	63.8 (21.3)	63.9 (17.5)	65.0 (20.5)
Stroop interference	25.9 (8.4)	28.0 (10.0)	27.8 (10.8)	29.4 (10.9)
UHDRS behavior				
Frequency	3.8 (3.7)	4.4 (4.5)	4.6 (4.5)	5.0 (5.0)
Frequency × severity	8.5 (10.0)	9.5 (12.2)	10.1 (11.2)	11.3 (15.8)

Values are mean (SD).

UHDRS = Unified Huntington's Disease Rating Scale.

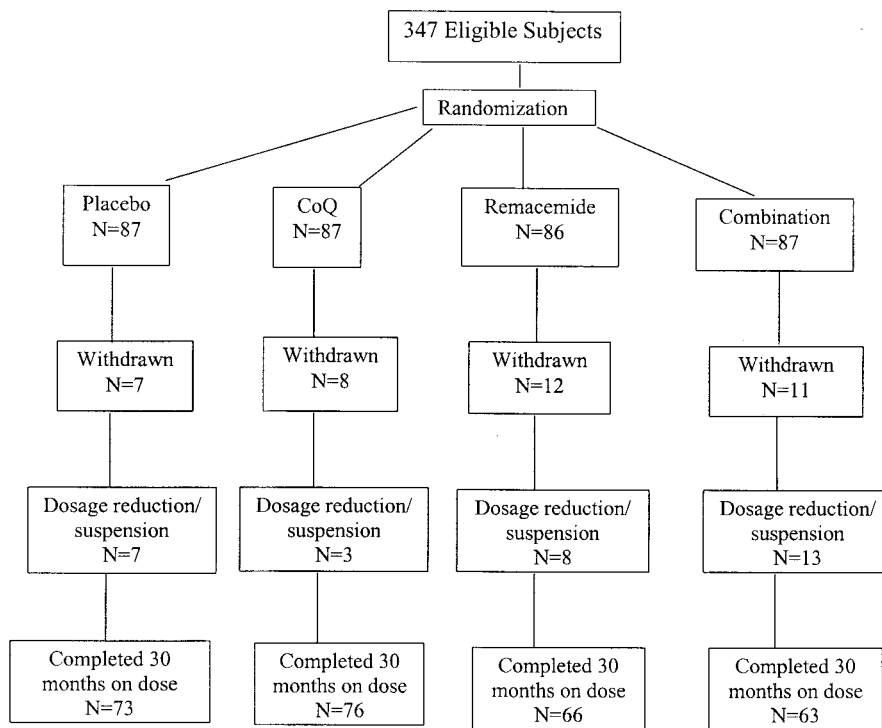


Figure 1. The flow of subjects through the trial is illustrated by treatment arm, including the number of subjects withdrawn, reducing the dosage of experimental intervention, and completing the trial on the assigned dosage.

total of 32 participants had early discontinuation of their study interventions (4 placebo, 4 coenzyme Q₁₀, 10 remacemide, 14 combined), and 9 of these participants (0 placebo, 2 coenzyme Q₁₀, 3 remacemide, 4 combination) later withdrew participation in the trial. The most common causes of early drug discontinuation were adverse experiences, principally psychiatric disturbances, nausea, vomiting, and

dizziness. In general, remacemide was not as well tolerated as coenzyme Q₁₀ and placebo.

Safety of interventions. Table 3 lists the common adverse events by treatment group with 92 to 95% of all research participants having encountered at least one adverse experience. The most commonly reported adverse experiences across all treatment groups included depres-

Table 3 Adverse events: number of subjects by treatment arm

Adverse event	Placebo, n = 87	Coenzyme Q ₁₀ , n = 87	Remacemide, n = 86	Combination, n = 87	p Values	
					C vs no C	R vs no R
Gastrointestinal						
Constipation	0	3	4	7	0.17	0.03
Nausea	9	13	27	22	0.90	0.0003
Stomach upset	2	8	7	13	0.03	0.06
Vomiting	3	7	13	10	1.00	0.02
Mood/cognition						
Cognitive decline	0	1	2	5	0.28	0.04
Depression	19	25	22	20	0.71	0.90
Moodiness	1	1	4	6	0.77	0.02
Neurologic						
Dizziness	5	4	13	12	0.72	0.004
Lightheadedness	4	2	5	12	0.39	0.02
Vision change	0	0	2	2	1.00	0.06
Body as a whole						
Headache	12	11	12	15	0.88	0.55
Sudden falls	28	29	19	20	0.91	0.04

C = coenzyme Q₁₀; R = remacemide.

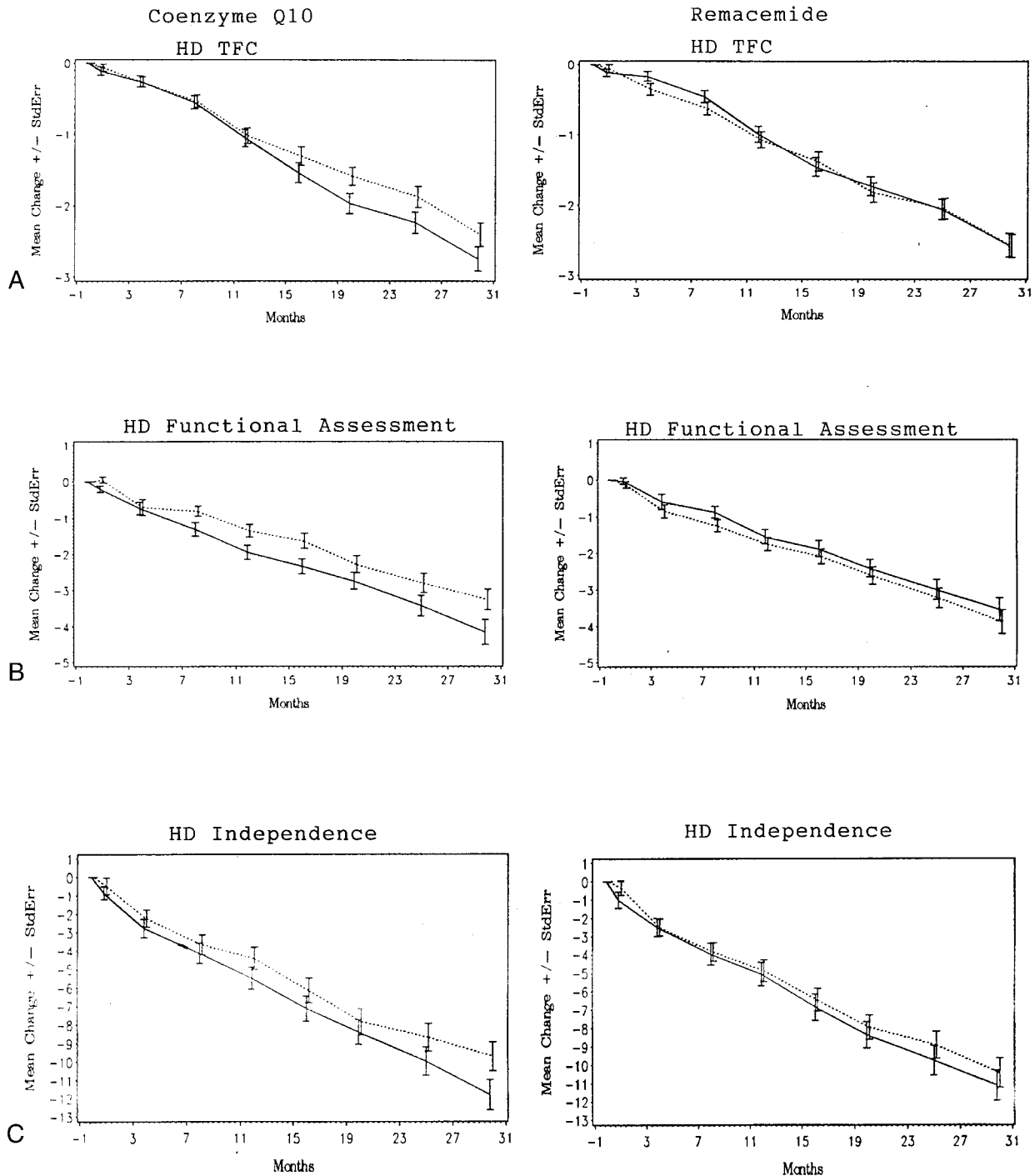


Figure 2. The graphs show the change from baseline value, over time, for (A) total functional capacity (TFC), (B) the functional assessment, and (C) the independence scale. The left column shows the treatment effect of Coenzyme Q₁₀ (dashed line) versus no Coenzyme Q₁₀ (solid line). The right column shows the treatment effect of remacemide (dashed line) versus no remacemide (solid line).

sion, sudden falls, nausea, headache, lightheadedness, and dizziness. Depression and headache were equally distributed across all the treatment groups. Dizziness, lightheadedness, nausea, and vomiting were all more likely to occur in the remacemide-treated groups, and sudden falls were less likely to occur in these groups. In addition, the less common adverse events of cognitive decline, constipation, and mood swings were more common in the remacemide-

treated groups. Stomach "upset" was reported more commonly in the coenzyme Q₁₀-treated groups.

Eighty-nine participants (25.6%) had at least one serious adverse experience (hospitalization, cancer, death), and these were similarly distributed among the treatment groups. The most common serious adverse event was hospitalization for psychiatric disturbances, principally depression with suicidal ideation. Unintentional overdoses of

Table 4 Treatment effects at 30 months

Outcome variable	Coenzyme Q ₁₀ effect, units (95% CI)	Remacemide effect, units (95% CI)
Primary outcome		
Total functional capacity	0.35 (−0.12, 0.82)	0.00 (−0.47, 0.47)
Secondary outcomes		
UHDRS functional		
Functional assessment	1.02 (0.18, 1.86)	−0.24 (−1.08, 0.59)
Independence scale	2.07 (−0.11, 4.26)	0.60 (−1.59, 2.78)
UHDRS motor		
Total	−0.01 (−2.35, 2.33)	−0.17 (−2.51, 2.17)
Maximal chorea	−0.10 (−1.05, 0.86)	−0.91 (−1.87, 0.04)
UHDRS cognitive		
Verbal fluency	0.23 (−1.11, 1.57)	0.84 (−0.49, 2.18)
Symbol digit	0.55 (−0.65, 1.76)	−0.06 (−1.25, 1.14)
Stroop color naming	2.65 (−0.59, 4.71)	0.77 (−1.29, 2.82)
Stroop word reading	2.17 (−0.35, 4.70)	−1.87 (−4.39, 0.65)
Stroop interference	0.95 (−0.64, 2.55)	−0.64 (−2.23, 0.95)
UHDRS behavioral		
Frequency	−0.68 (−1.56, 0.21)	0.22 (−0.67, 1.11)
Frequency × severity	−2.30 (−4.93, 0.31)	1.30 (−1.32, 3.92)
Supplemental neuropsych		
HVL–Total Recall	−0.36 (−1.22, 0.50)	0.12 (−0.74, 0.98)
Brief Test of Attention	0.74 (0.13, 1.36)	−0.24 (−0.85, 0.38)
Trailmaking A	−0.32 (−10.50, 9.84)	1.67 (−8.54, 11.88)
Trailmaking B	−1.93 (−13.53, 9.67)	0.35 (−11.18, 11.88)
CALT–Trials	−1.73 (−4.85, 1.40)	−0.66 (−3.78, 2.47)
CALT–Errors	−1.16 (−5.60, 3.29)	−1.54 (−5.98, 2.90)

Coenzyme Q₁₀ effect is the difference in mean change between the groups [(combination + CoQ) − (remacemide + placebo)] adjusted for center and the baseline value of the outcome variable in an analysis of covariance model (see text for details). The remacemide effect is similarly defined.

UHDRS = Unified Huntington's Disease Rating Scale; HVL = Hopkin's Verbal Learning; CALT = Conditional Associative Learning Test.

study medications and hospitalizations for other disorders made up the remainder of these events. Three deaths occurred during the study, one in the placebo group (asthma), one in the coenzyme Q₁₀ group (fall), and one in the combined treatment group (suicide), the last occurring more than 30 days after prematurely discontinuing study interventions.

Efficacy of interventions. The average decline in TFC in the placebo group was higher than we had projected in our sample size calculation (2.74 versus 1.25 units), but was consistent with longitudinal data from other sources that demonstrate a decline of about 1 unit per year.¹⁵⁻¹⁷

There were no significant differences between the treatment groups for the change in TFC score between baseline and 30 months, the primary response variable. There was 13% slowing of TFC decline in the coenzyme Q₁₀-treated groups whereby coenzyme Q₁₀-treated participants declined by 2.40 ± 2.14 TFC units compared with the participants who did not receive coenzyme Q₁₀ who declined by 2.74 ± 2.28 units ($p = 0.15$, table 4, figure 2A). Coenzyme Q₁₀ exerted a nominally significant effect in slowing func-

tional decline (22% slowing) as measured by the functional assessment checklist ($p = 0.02$, figure 2B) and a trend toward slowing functional decline (18% slowing) on the independence scale ($p = 0.06$, figure 2C). Remacemide had no apparent impact on the TFC rate of decline or on other measures of functional decline (table 4, figure 2, A through C). (Additional data regarding the 30-month changes in all outcome variables are available online at www.neurology.org).

Coenzyme Q₁₀ had a trend toward a beneficial impact on two of the cognitive tests (table 4)—Stroop (color naming, $p = 0.01$; word reading, $p = 0.09$) and Brief Test of Attention ($p = 0.02$). There was also a trend toward a beneficial impact of coenzyme Q₁₀ on behavior (behavior frequency, $p = 0.14$; frequency × severity, $p = 0.08$). Remacemide tended to have a beneficial impact on the chorea subscale of the UHDRS motor scale ($p = 0.06$, table 4). No treatment effects were observed on other outcomes (table 4).

There was no worsening (either significant or trends) in any of the outcome measures in the coenzyme Q₁₀ group.

There was no evidence that the treatment effects varied significantly among the 23 centers. Treatment effects were similar for men and women. There was, in general, no evidence of an interaction between the two interventions. The initiation of antidepressant, antipsychotic, and anxiolytic medications was the same among the treatment groups. The mean compliance (assessed by pill counts) with both experimental interventions ranged from 85 to 90% across all treatment groups.

Discussion. This controlled trial of coenzyme Q₁₀ and remacemide in early HD demonstrated no significant impact on functional decline as measured by the TFC scale, the prespecified primary outcome. There was a trend toward a smaller decline in the TFC among participants treated with coenzyme Q₁₀ compared with those who were not treated with coenzyme Q₁₀. The difference between the groups was not evident at the first visit but emerged after approximately a year of treatment, although there was no clear continuing separation (figure 2A). This observation argues against an acute symptomatic effect of coenzyme Q₁₀ to explain the trend toward slower disease progression. This trend toward a slower decline with coenzyme Q₁₀ treatment was also observed in the two additional measures of function, in two of the cognitive tests, and in the behavioral scale of the UHDRS. This is the first controlled trial in HD to find trends toward a beneficial change in functional decline. Coenzyme Q₁₀ treatment has previously been reported to cause a potentially beneficial biologic effect in patients with HD, namely reduction in elevated brain lactate² and decreased lesion size in animal models of HD.³ Coenzyme Q₁₀ was not associated with worsening of any of the outcome variables and was exceedingly well tolerated.

The remacemide-treated group had a trend toward reduced chorea that appeared rapidly and was sustained. A similar result was seen in an earlier trial of remacemide.⁷ These findings are consistent with effects of other agents that retard glutamate transmission and attenuate chorea.¹⁸ They lend support to the notion that antiglutamatergic therapies exert antichoreic effects and may be useful in place of, or in addition to, dopamine blocking or depleting agents (e.g., neuroleptics, tetrabenazine). Remacemide was associated with clinical adverse events, particularly dizziness and nausea, the most common side effects identified in prior controlled trials. Although preclinical evidence supported the use of an intervention like remacemide, the drug had no impact on functional decline. This failure may have been due to insufficient dosage, unfavorable receptor selectivity, or inappropriate stage of HD; however, it is also possible that glutamatergic toxicity does not play a major role in the pathogenesis of HD.

Previous studies of interventions designed to slow functional decline, including baclofen,¹⁴ idebenone,¹⁹ vitamin E,²⁰ and lamotrigine,¹⁷ have found no significant impact on functional decline. This study was designed with a larger number of participants and

longer clinical follow-up in an effort to identify an approximate 35 to 40% slowing in functional decline. We have excluded a benefit of that magnitude with a reasonable degree of confidence, although we observed trends toward a smaller benefit that may be of clinical significance. Placebo-controlled, dosage-ranging trials of coenzyme Q₁₀ are still warranted in patients with early HD. The feasibility of conducting another large, placebo-controlled trial of coenzyme Q₁₀ is not clear because approximately 1,600 participants would be required in a 2-arm trial to confirm an effect of the magnitude observed in this study. It is not appropriate to extrapolate these observations to patients in the later stages of HD or to asymptomatic individuals at risk for HD. Placebo-controlled studies of coenzyme Q₁₀ also seem warranted in the latter population.

The current findings are not sufficient to warrant a recommendation for coenzyme Q₁₀ treatment of early HD. The benefits of coenzyme Q₁₀ we have observed in slowing functional decline are small at best, and we do not know whether they are reproducible or could be sustained, if real. The risks of coenzyme Q₁₀ over 30 months seem negligible. The financial costs can be considerable, currently ranging from 60 to 150 US dollars per month for the dosage studied. Clinicians should also be cognizant that coenzyme Q₁₀ is a nutritional supplement and not subject to the same quality and content regulations as pharmaceuticals.

Appendix

Huntington Study Group authors of this report include the following:

Steering Committee: K. Kieburtz (Principal Investigator), University of Rochester; W. Koroshetz (Co-Principal Investigator), Massachusetts General Hospital; M. McDermott (Biostatistician), University of Rochester; M.F. Beal, Cornell Medical Center; J.T. Greenamyre, Emory University; C.A. Ross, Johns Hopkins University; I. Shoulson, University of Rochester.

Participating Investigators/Coordinators (affiliation at time of study): M.E. Cudkovic, P. Sexton, C. Skeuse, D. Rosas, B. Jenkins, Massachusetts General Hospital; A. Rosenblatt, M. Sherr, Johns Hopkins University; S. Hersch, J. Cellar, Emory University; M. Guttman, C. Brown, University of Toronto; P.G. Como, F. Marshall, J.A. DeMarcaida, C. Zimmerman, University of Rochester; K. Marder, C. Moskowitz, C. Polanco, J. Beltre, Columbia University; K. Shannon, J.A. Jaglin, F. Niederman, Rush-Presbyterian/St. Luke's Medical Center; T. Ashizawa, C. Hunter, C. Hunter, Baylor College of Medicine; R. Hauser, A. Walker, L. Gauger, M. A. Hahn, H. Delgado, University of Southern Florida; T. Dawson, Johns Hopkins University; E. Siemers, Indiana University; L. Seeberger, C. Dingmann, Colorado Neurological Institute; R. Dubinsky, C. Gray, University of Kansas; W.J. Weiner, D. Rodriguez-Bateman, University of Miami; R.L. Albin, K. Wernette, University of Michigan; M. Harrison, E. Rost-Ruffner, University of Virginia; J. Paulsen, R.L. Rodnitzky, J. Dobson, L. Vining, University of Iowa; O. Suchowersky, C. Pantella, University of Calgary; M.H. Saint-Hilaire, J. Furtado, Boston University; W. Martin, M. Wieler, University of Alberta; F. Walker, V. Hunt, Wake Forest University; L. Raymond, E. Almqvist, University of British Columbia; A. Rubin, B. Blair, Hahnemann University; K. Marek, K. Caplan, Yale University.

Biostatistics/Coordination Centers Staff: D. Baker, A. Brocht, C. Casaceli, C. Orme, A. Rudolph, L. Rumfola, G. Schifitto, A. Shinaman, K. Sulimowicz, A. Watts, S. Eapen, L. Zhang, University of Rochester.

Safety Monitoring Committee: P. Tariot (Chair), University of Rochester; S. Fahn, Columbia University; W. Hall, University of Rochester.

PSMB Committee: W. Koller, (Chair), J. Gorell, R. Woolson.

NIH-NINDS (Sponsor): E. Oliver.

AstraZeneca (provided monitoring support, supply of drug and placebo): A. Allen, A.M. Craun, J. McDermott, R. McKinley, E. Means, L. Rexo, E. Wratni.

Vitaline (provided partial support by formulating coenzyme Q₁₀): J. Meese.

Neuropsychology Consultant: J. Saint-Cyr, University of Toronto.

References

1. Dure LS, Young AB, Penney JB. Excitatory amino acid binding sites in the caudate nucleus and frontal cortex of Huntington's disease. *Ann Neurol* 1991;30:785-793.
2. 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.
3. Beal MF, Henshaw DR, Jenkins BG, Rosen BR, Schulz JB. Coenzyme Q₁₀ and nicotinamide block striatal lesions produced by the mitochondrial toxin malonate. *Ann Neurol* 1994;36:882-888.
4. Browne SE, Bowling AC, MacGarvey U, et al. Oxidative damage and metabolic dysfunction in Huntington's disease: selective vulnerability of the basal ganglia. *Ann Neurol* 1997;41:646-653.
5. Lodi R, Schapira AHV, Manners D, et al. Abnormal in vivo skeletal muscle energy metabolism in Huntington's disease and dentatorubropallidolusian atrophy. *Ann Neurol* 2000;48:72-76.
6. Kieburtz K, Feigin A, McDermott M, et al. A controlled trial of remacemide hydrochloride in Huntington's disease. *Mov Disord* 1996;11:273-277.
7. Feigin A, Kieburtz K, Como P, et al. Assessment of coenzyme Q₁₀ tolerability in Huntington's disease. *Mov Disord* 1996;11:321-323.
8. Shoulson I, Fahn S. Huntington's disease: clinical care and evaluation. *Neurology* 1979;29:1-3.
9. Huntington Study Group (Kieburtz K). Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord* 1996;11:136-142.
10. Brandt J. The Hopkins Verbal Learning Test: development of a new memory test with six equivalent forms. *Clin Neuropsychologist* 1991;5:125-142.
11. Schretlen D, Bobholz JH, Brandt J. Validation of the brief test of attention in patients with HD and amnesia. *Clin Neuropsychologist* 1996;10:90-95.
12. Reitan RM, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery. Tuscon: Neuropsychology Press, 1958.
13. Petrides M. Nonspatial conditional learning impaired in patients with unilateral frontal but not unilateral temporal lobe excisions. *Neuropsychologia* 1990;28:137-149.
14. Shoulson I, Odoroff C, Oakes D, et al. A controlled clinical trial of baclofen as protective therapy in early Huntington's disease. *Ann Neurol* 1989;25:252-259.
15. Penney JB Jr, Young AB, Shoulson I, et al. Huntington's disease in Venezuela: 7 years of follow-up on symptomatic and asymptomatic individuals. *Mov Disord* 1990;5:93-99.
16. Marder K, Zhao H, Myers RH, et al. Rate of functional decline in Huntington's disease. *Neurology* 2000;54:452-458.
17. Kremer B, Clark CM, Almqvist EW, et al. Influence of lamotrigine on progression of early Huntington disease. A randomized clinical trial. *Neurology* 1999;53:1000-1011.
18. Rosas HD, Koroshetz WJ, Jenkins BG, et al. Riluzole therapy in Huntington's disease (HD). *Mov Disord* 1999;14:326-330.
19. Ranen NG, Peyser CE, Coyle JT, et al. A controlled trial of idebenone in Huntington's disease. *Mov Disord* 1996;11:549-554.
20. Peyser CE, Folstein M, Chase GA, et al. Trial of d- α -tocopherol in Huntington's disease. *Am J Psychiatry* 1995;152:1771-1775.

Access *www.neurology.org* now for full-text articles

Neurology online is now available to all subscribers. Our online version features extensive search capability by title key words, article key words, and author names. Subscribers can search full-text article *Neurology* archives to 1999 and can access link

references with PubMed. The one-time activation requires only your subscriber number, which appears on your mailing label. If this label is not available to you, call 1-800-638-3030 (United States) or 1-301-714-2300 (outside United States) to obtain this number.