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# Coenzyme Q10: A Review of Its Promise as a Neuroprotectant

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**Needs Assessment**
There is great interest in coenzyme Q10 as a potential treatment for Parkinson's disease, Huntington's disease, and other neurodegenerative diseases. This review article provides a comprehensive knowledge and current dosing tolerance of coenzyme Q10 to date, from promising published clinical trials though most have tended to be pilot studies.

**Learning Objectives**
At the end of this activity, the participant should be able to:
- List the function of coenzyme Q10 in the mitochondria.
- Discuss the clinical evidence of the function of coenzyme Q10.
- Give scientific evidence of the effects of coenzyme Q10.
- List some drug-drug interactions of coenzyme Q10.
- Understand the possible side effects of coenzyme Q10..

**Target Audience:** Neurologists and psychiatrists

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This activity has been peer-reviewed and approved by Eric Hollander, MD, chair at the Mount Sinai School of Medicine. Review date: December 8, 2006. Dr. Hollander does not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

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# Faculty Affiliations and Disclosures

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# Abstract

*Coenzyme Q10 (CoQ10) is a powerful antioxidant that buffers the potential adverse consequences of free radicals produced during oxidative phosphorylation in the inner mitochondrial membrane. Oxidative stress, resulting in glutathione loss and oxidative DNA and protein damage, has been implicated in many neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and Huntington's disease. Experimental studies in animal models suggest that CoQ10 may protect against neuronal damage that is produced by ischemia, atherosclerosis and toxic injury. Though most have tended to be pilot studies, there are published preliminary clinical trials showing that CoQ10 may offer promise in many brain disorders. For example, a 16-month randomized, placebo-controlled pilot trial in 80 subjects with mild Parkinson's disease found significant benefits for oral CoQ10 1,200 mg/day to slow functional deterioration. However, to date, there are no published clinical trials of CoQ10 in Alzheimer's disease. Available data suggests that*

*oral CoQ10 seems to be relatively safe and tolerated across the range of 300–2,400 mg/day. Randomized controlled trials are warranted to confirm CoQ10's safety and promise as a clinically effective neuroprotectant.*

# Introduction

There is significant interest in exploring the use of antioxidants for the potential treatment of neurodegenerative disorders. Prior therapeutic research has focused on agents, such as tocopherol, and monoamine oxidase inhibitors as neuroprotectants.[1] Coenzyme Q10 (CoQ10) may also be a promising neuroprotectant. Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders were found to have defects in the inner mitochondrial membrane and in oxidative phosphorylation.[2] A decrease in CoQ10 levels and in complex I activity have also been reported; leading to the hypothesis that such changes may play a role in the pathogenesis of neuronal damage.[3] Other antioxidants, such as selegiline (a selective monoamine oxidase inhibitor), have been tested in both Parkinson's disease and Alzheimer's disease.[4,5] Clinical trials of vitamin E were first conducted in Parkinson's disease and based on these data; it was then tested in Alzheimer's disease.[4] Because the researchers reported that elderly patients often take CoQ10 on their own, this article reviews the rationale and current clinical evidence for CoQ10 as a therapeutic neuroprotectant.

# What is Coenzyme Q10?

CoQ10 is an endogenous proenzyme found in the inner mitochondrial membrane of human cells.[6] It is a fat-soluble quinone that in human tissue has 10 five-carbon isoprenoid units, hence the term CoQ10. It is normally involved in a series of enzymatically catalyzed sequential reactions necessary to carry out oxidative phosphorylation via the electron transport chain (ETC), which also known as the respiratory chain. It collects reducing electrons from flavoprotein. Oxidative phosphorylation is an essential process used in the production of energy to sustain organs such as the brain, heart, muscles, and kidneys through the production of adenosine triphosphate (ATP).[6,7]

Redox reactions in the inner-mitochondrial membrane are a series of sequential biochemical interactions, that are traditionally referred to as complexes, the most important being complex I, which comprises CoQ10.[6] While CoQ10 is not the first coenzyme with which electrons react, it is the first coenzyme with which all electrons must react in order to progress the chemiosmatic gradient along the ETC.[6] CoQ10, therefore, plays a vital role in the efficiency of the ETC and energy production.[6-8] The sequencing of the complexes as they donate electrons to oxygen is nicotinamide adenine dinucleotide, flavoproteins, CoQ10, and cytochromes b, $c_1$, c, a, $a_3$. Redox-reaction and the chemiosmotic gradient in the ETC were delineated in 1961 and later recognized by a Nobel prize.[9]

# Experimental Studies of Coenzyme Q10

There is evidence from preclinical studies that suggest CoQ10 may be a neuroprotectant. For example, CoQ10 has been reported to inhibit atherosclerosis in the apolipoprotein E (ApoE) knockout mouse

model.[10,11] It has been shown to inhibit oxidative stress in mice and in vitro, and diminish damage to the hippocampus following carotid ligation or toxic injury.[12] In addition, endothelin models of cerebral ischemia in rats demonstrated the neuroprotective effects of CoQ10 on lactate acidosis, ATP production, oxidized and reduced glutathione ratio, and super oxide dismutase activities after induced cerebral ischemia.[13]

CoQ10 showed promise after neuronal insult in a controlled experiment with 206 male wistar rats randomized to three-paired groups.[13] Isoforms of endothelins, (potent vasoconstrictors) endothelin 1 or endothelin 3 were administered intracerebroventricularly. One group received endothelin 1 or endothelin 2 intracerebroventricularly in addition to CoQ10 10.0 mg/kg in 0.5 ml soybean oil IP. A control group received Ringer's solution plus soybean oil only, while a norm group was administered no procedure. Examination of the rats' right and left cerebral hemispheres at 1-, 4-, and 24-hour intervals after exposure to the potent vasoconstrictors showed that the groups receiving CoQ10 made an earlier recovery and had a decrease in neuronal injuries with fewer foci in the cerebral cortex and hippocampus.[13]

In a similar 10-week study with 80 male wistar rats randomized to eight groups,[12] the effects of CoQ10 on neuronal damage and loss was explored in rat hippocampus and dentate gyri, and on a key apoptotic enzyme, caspase-3 (CPP32) after induced diabetic and ischemic injury. To induce oxidative stress, injections with steptozotocin were used to cause diabetes. Air injected into the left carotid, followed by bilateral ligation of the common carotid arteries produce cerebral ischemia.[12] In this model, pre-treatment with CoQ10 10 mg/kg IP for 7 days led to significant decrease in neuronal loss due to ischemia and reduced activity of a key enzyme (CPP32) involved in apoptotic cell death.[12] The decrease in neuronal damage varied among groups. In the experimental groups with induced diabetes only, there was a decrease of 80%, compared with a 33% decrease in ischemic rats only and a 53% decrease among those with combined diabetes and ischemia. CoQ10 decreased CPP32 activities in all experimental groups.[12] These experiments demonstrated the effects of CoQ10 as a potent antioxidant and free radical scavenger in the hippocampus and dentate gyri. The results also suggest that CoQ10 may be effective in blocking CPP32 activities, which is postulated be a key enzyme in the apoptotic pathway of neuronal cell death.[12] Although findings from this study are promising, limitations of this experiment are that it is unknown if results can be generalized to neurons in other nuclei in the brain or if the significantly different biochemical or histological differences observed, can be correlated with functional differences. An argument can be made for a high likelihood of correlation, given that significant differences were observed both in preclinical and clinical studies. Longer studies with larger populations can help to establish the strength of associations of CoQ10 as a neuroprotectant as well as to judge it's potential clinical relevance over time. Clinical studies in patients with cerebral ischemia (eg, vascular dementia, diabetes) would also be useful to test these findings in humans,

Ren and colleagues,[14] explored the effects of CoQ10 on 16 dogs that underwent deep hypothermic circulatory arrest with cardiopulmonary bypass to mimic a clinical bypass procedure. The results showed that dogs pre-treated with CoQ10 had higher levels of ATP and greater protection of the cortex from structural damage. Of interest, the experimental group had significantly less free radical formation at 60 minutes after the arrest and at 30 minutes into reperfusion than control. Combined, the results from these studies suggest that CoQ10 shows promise as a potent antioxidant and as a free radical scavenger. Oxygen-derived free radicals and abnormal energy metabolism play a role in brain ischemia/reperfusion injury and that CoQ10 exerted a neuron-protective effect by improving brain energy metabolism and diminishing ischemic damage.[14]

# Clinical Trials of Coenzyme Q10 in Brain Disorders

CoQ10 levels and therapeutic effects have been tested in pilot studies of Parkinson's disease and Huntington's disease.[15-17] Lower levels of CoQ10 and decreased activities of complex I were found in brains and platelets of 15 Parkinson's disease patients compared with age/sex-matched controls (Table 1).[18] The authors also found a positive correlation between levels of CoQ10 and levels of the activities of complex I and II/III. CoQ10 was reportedly well absorbed with oral administration.[18] The researchers suggested that the effects of CoQ10 might potentially slow the deterioration in the nigrostratal dopaminergic system.[18] The small sample size, short duration, and lack of efficacy correlates are limiting factors in this study.

**TABLE 1.**
**Review of Clinical Trials with CoQ10**

| *Design* | *Treatment Groups* | *Results* |
|---|---|---|
| National, multicentered, randomized, parallel-group, controlled study (N=80) for 16 months | 4 groups of patients with PD received varying dosages of CoQ10: placebo, 300, 600, 1,200 mg/day | Improved functional symptoms, changes in total UPDRS scores: +11.9, +8.81, +10.8, +6.86, respectively; Maximum benefit from 1,200 mg/day |
| Multicentered, parallel-group, placebo-controlled, double-blind study (N=38) CoQ10 360 mg/day for 4 weeks | Stable patients with PD treated with CoQ10 360 mg/day for 4 weeks | Farnsworth-Munsell 100 Hue test showed significantly improved visual symptoms compared with control (P=.008) |
| Pilot study, age/sex matched, controlled (N=15) | Patients with PD and HD, correlated CoQ10 levels with complex I, II, and III activities in brain and platelets of 15 patients | Higher levels of CoQ10 positively correlated with levels of complex I, II, and III activities |
| Open-label trial, CoQ10 300–1,200 mg/day (N=9) for 4 years | Patients with Friedreich's ataxia and LVH treated with CoQ10 400 mg/day and vitamin E 2,100 IU/day | Cardiac function improved after 2 years, 50% ↑ in cardiac energy metabolism, 34% ↑ in skeletal muscle ATP production lack of neurodegenerative progress |

CoQ10=coenzyme Q10; PD=Parkinson's disease; UPDRS=Unified Parkinson Disease Rating Scale; HD=Huntington's disease; LVH=Left ventricular hypertrophy; ATP=adenosine triphosphate.

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The efficacy and safety of CoQ10 was explored in a 16-month randomized, double-blind, parallel-group, placebo-controlled trial with 80 subjects who had mild Parkinson's disease.[3] Subjects attended a movement disorder clinic at the time of enrolment, and these subjects were able to perform their normal activities of daily living. Subjects were randomized to oral CoQ10 300 mg/day, 600 mg/day, 1,200 mg/day, or placeb, over a 16-month period, or until they required rescue treatment. Using the Unified Parkinson Disease Rating Scale (UPDRS), analysis measured the difference in total scores between baseline and at end of the study.[3] Results revealed that the subjects who received the highest dosing also received the greatest benefit, and experienced a slower decline as measured by the UPDRS. Adjusted mean total change was +11.99, +8.8, +10.82, and +6.69 for placebo, 300 mg/day, 600 mg/day, and 1,200 mg/day, respectively. Primary analysis looking for a dose-related trend was significant ($P$=0.09), which met their pre-specified criteria. In addition, a secondary analysis showed that 1,200 mg/day dose was superior to placebo. The study reported good tolerability of CoQ10 with mild gastrointestinal upset.[3] This well-designed clinical trial was limited mainly by the small sample size; the authors[3] acknowledged the need to confirm these findings in a larger trial.

An open-label pilot study[19] examined blood levels and tolerability of higher doses of CoQ10 in 17 patients with mild Parkinson's disease. Escalating daily doses of CoQ10 at 1,200 mg/day, 1,800 mg/day, 2,400 mg/day, and 3,000 mg/day were administered with vitamin E 1,200 IU daily. Maximum exposure was 2 months with 1 month at 2,400 mg/day or 3,000 mg/day. CoQ10 levels were measured after each dose and reached a plateau at 2,400 mg/day. The 3,000 mg/day dose was achieved by 13 of 17 patients.[19] Side effects noted that were possibly related to study drug include a case of dyspepsia, asymptomatic mild

hypocalcemia, and mild creatine kinase elevations. Other side effects, which investigators felt were not related or were uncertain, included one case each of cognitive change, chest pain, paroxysmal atrial tachycardia, and orthostasis. The small sample size, short duration, and open design were limitations and did not permit conclusive assessment of safety or efficacy. Based on plasma levels, the investigators concluded, that the 2,400 mg/day dose could be an optimal higher dose to test in future efficacy studies.

Visual dysfunction is another known feature of Parkinson's disease that is associated with a decrease in CoQ10 levels.[20] In a pilot multicenter, double-blind, placebo-controlled, clinical trial, CoQ10, 360 mg/day for 4 weeks administered to 38 stable patients was shown to be effective in improving visual symptoms.[20] As evaluated by the Farnsworth-Munsel 100 Hue test (a test for measuring visual acuity), results showed that patients treated with CoQ10 had significantly improved visual symptoms.[20]

In another pilot study (N=15),[3] the biochemical effects of three different dosages of CoQ10 were studied in patients who suffer with Parkinson's disease. Dosages of 200 mg, 600 mg, and 800 mg/day were given for 1 month. Results showed that patients treated with CoQ10 performed better on the UPDRS compared with those receiving placebo, and that CoQ10 was well tolerated. The authors reported that while CoQ10 did not have an effect on the motor portion, of the UPDRS, there were trends toward an increase in complex I activity.

Not all clinical trials have reported positive results of CoQ10 in the treatment of Parkinson's disease.[21] For example, in an open-label trial with 10 Parkinson's disease patients treated with CoQ10, 200 mg/day for 3 months, the results revealed no significant differences in motor function after treatment.[21] The UPDRS sum scores evaluated the motor functions, measuring bradykinesia of hands, and walking. There were also no significant side effects.[21] This study like many others demonstrates that effective therapy with CoQ10 may require higher dosages and for possibly longer duration in order to achieve more desirable effects. This may indicate that the effects of CoQ10 are dose-dependent, or that different symptoms are affected by different dosages. One study reported a moderately significant difference on visual symptoms with just 360 mg/day for 1 month,[20] while some moderately higher dosages for longer periods had no effect on neurological symptoms.[3] A pilot trial[19] reported yet higher doses achieved some effect on neurological symptoms, as demonstrated in Table 1.

# Clinical Studies in Huntington's Disease

Although the pathophysiology of Huntington's disease is not well understood, a deficiency of CoQ10 was identified as a part of the disease process.[15] The autosomal dominant disorder exhibits neuronal degeneration that predilects to the basal ganglia, brainstem, and cerebral cortex.16 Previous studies[16] have demonstrated that patients with Huntington's disease who are treated with CoQ10 often show a reduction in otherwise elevated lactate levels in the basal ganglia and an increased activity of complex I, implicating a pathophysiological defect in mitochondrial energy metabolism. To evaluate the efficacy and tolerability of CoQ10, a 6-month open-label, clinical trial treated 10 subjects with CoQ10 300–1,200 mg/day. Results revealed no significant changes in these patients. Patients were evaluated at baseline, at 3 months, and at 6 months using the Huntington Disease Rating Scale, the Huntington Disease Functional Capacity Scale, and standardized neuropsychological measures.[16] The study showed good tolerability. Patients showed mild adverse effects, predominantly gastrointestinal upset. The lack of significant results may be attributed to methodological limitations, which included a small sample size and insufficient subject randomization. Because only one of 10 patients took 1,000 mg/day, another 1,200 mg/day, and all took 600 mg, the results

may be more reflective of effects of 600 mg/day rather than 1,200 mg/day.

# Clinical Studies on Friedreich's Ataxia

CoQ10 has also shown a small promise in patients with the most common type of ataxia, Friedreich's ataxia.[23,24] The disorder exhibits cardiomyopathy and characteristic neurological symptoms, such as limb and gait disturbances, in addition to behavioral symptoms.[25,26] The genetic defect in Friedreich's ataxia is most often due to a point deletion or a gene expansion of the Friedreich's ataxia gene *13q*, subsequently leading to a significantly decreased mitochondrial protein, frataxin.[26] The loss of function of frataxin consequently leads to increased oxidative stress.[26] The insult affects complex I through III, diminishing the level of energy metabolism of the muscles, to include cardiac muscles, skeletal muscles, and contributing to neurotoxicity.[13,25] Though studies have suggested CoQ10 may be effective in treating cardiac muscle, mitochondrial activities and left ventricular hypertrophy,[12,14,26,27] results have been less promising with regards to improvements in neurological function.[24] Lordi and colleagues[24] conducted a 4-year open-label, controlled clinical trial. Nine patients with Friedreich's ataxia and left ventricular hypertrophy were treated with CoQ10 400mg/day and vitamin E 2,100 IU/day. Results yielded a 50% increase in cardiac phosphocreatine: ATP ratio, an indicator of energy metabolism,; and a 34% increase in skeletal muscle Vmax for ATP production. Results only achieved a lack of neurological progression as measured by the semi-quantitative International Cooperative Ataxia Rating Scale.[24] Optimistically, these patients showed a sustained lack of neurodegenerative progression and an improvement in cardiac function after a 2-year follow-up.[3,24]

Other trials[20,27-29] as well as a 1-year open-label trial with CoQ10 5 mg/kg/day[30] administered to eight patients with Friedreich's ataxia showed significant improvements in cardiac symptoms with treatment of CoQ10. The authors reported no significant effect on improving neurological dysfunctions in patients with Friedreich's ataxia.[25,30]

# Case History of Familial Coenzyme Q10 Deficiency

CoQ10 demonstrated significant efficacy in reducing apoptosis, and completely reversed clinical symptoms in two patients with myopathic mitochondrial deficiency.[31] Di Giovanni and colleagues reported a case history of two male siblings 12 and 15 years of age, who presented with multiple symptoms, such as exercise intolerance, myoglobinurea, muscle disease, and toxic heart failure, that demonstrated sequelae of CoQ10 deficiency. Abnormal electromyography showed features of myopathy, and the younger sibling exhibited episodes of seizure. Treatment with ubidecarenone (a short chain homologue of CoQ10 150 mg/day, titrated up to 200–300 mg/day, resulted in normal CoQ10 levels after 8 months of therapy with CoQ10.31 Histochemical and immunohistochemical assays performed before treatment and at 2 months and 8 months after the initiation of treatment resulted in normalization of creatine kinase levels (byproduct of muscle breakdown) and lactic acid levels (indicator of oxidative stress), and remained normal after 3 years of follow-up.[31] The design of the experimental treatment in these two subjects has provided strong evidence that CoQ10 directly affects apoptosis, oxidative stress, the opening of mitochondrial permeability transition pores, and neurotoxicity.[31]

## Alzheimer's Disease

To date, there are no published clinical trials of CoQ10 in Alzheimer's disease. The reasons for this are primarily related to funding which would have to come from either the National Institutes of Health-Office of Complementary and Alternative Medicine, private foundations or supplement manufacturers. A model that could be utilized is that of ginkgo biloba where both treatment studies in Alzheimer's disease and vascular dementia as well as primary prevention trials have been conducted through funding from the National Institutes of Health and private industry. An ideal treatment trial would be a three-arm study comparing CoQ10 with donepezil and placebo over 6 months in mild to moderate Alzheimer's disease. However, one logistic difficulty with such a design would be the logistic difficulty in recruiting treatment-naïve Alzheimer's disease patients. Hence, an alternative design may be to conduct an add-on augmentation trial of CoQ10 versus placebo in Alzheimer's disease patients on stable cholinesterase inhibitor therapy. Such a study would need relatively large sample sizes (perhaps 300/arm) and may cost $3–7 million. A prevention trial in individuals at risk for Alzheimer's disease (either by virtue of age, family history, mild cognitive impairment status, or ApoE status) could mimic the ginkgo prevention trial (primary prevention model) or the vitamin E mild cognitive impairment trial (secondary prevention model). Such studies would also cost millions of dollars. The available evidence would suggest that a treatment trial is warranted.

# Safety and Efficacy of Coenzyme Q10

Results from all studies reviewed reported relatively good tolerability of CoQ10 when taken in dosages ranging from 200–3,000 mg/ day. One study has found that plasma levels appear to plateau at 2,400 mg/day A cumulative report included mild side effects, such as headache, heartburns and other gastrointestinal symptoms.[17,20,25] Among other reported side effects were fatigue, increased involuntary movements, and asymptomatic elevated liver enzymes. Contraindications or caution should be taken with patients who suffer certain comorbidities, as outlined in the Table 2. Currently, CoQ10 is marketed as a nutraceutical and therefore has not yet been evaluated by the Food and Drug Administration for any specific disease treatment or prevention efficacy claims. Consumers must be aware that potentially, there may be quality differences and variations among brands both in the potency and the purity of the product. No dose recommendations can be made at this time and larger clinical trials are warranted to determine a reliable effective recommended daily dosing for corresponding indications.

**TABLE 2.**
**Potential Drug Interactions/Cautions with CoQ10***

| Drugs | Interactions/Cautions |
|---|---|
| β-blockers | CoQ10 may have a positive inotrophic effect[10,11] CoQ10 has been postulated to lower blood pressure[10,11] and there is a potential for hypotension |
| HMG CoA reductase inhibitors | HMG CoA reductase inhibitors has been shown to decrease CoQ10 serum content[10] therefore concomitant use may warrant higher doses of Co Q10 to maintain effectiveness |
| Anti-diabetic agents | CoQ10 is postulated to have a synergistic effect with anti-diabetic agents and hence there is a potential risk of hypoglycemia[8] |
| Coumadin | CoQ10 is postulated to have an inhibiting effect on coumadin. This may be explained by the similarity of the structures of CoQ10 and vitamin K[12] |

* CoQ10 seems relatively safer with regards to drug interactions than most prescription drugs.

CoQ10=coenzyme Q10; HMG CoA=3-hydroxy-3-methyl-glutaryl-CoA

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Currently, multiple manufacturers market CoQ10 (eg, Oleomed Cell-Q Formula, Preventive Nutrition Coenzyme Q-10, Q-Gel Forte, Ubiqgel, CoQ10) as soft gels, capsules, tablets, and in liquid form. A 1-month supply varies from $15.00–45.00 depending on dosage and quantity. Higher dosages, such as 1,200 mg/day, may cost ~$8.00–$10.00/day. CoQ10 is a fat-soluble quinone, thus theorized to have better bioavailability in an oil-based preparation, or when administered with foods of higher fat content.

# Conclusion

A review of the literature in MEDLINE resulted in no previous clinical trials in patients with Alzheimer's disease and CoQ10. However, there is limited pilot evidence to show that oral treatment with CoQ10 increases its plasma levels, and modestly decreases neurological symptoms in patients with Parkinson's and Huntington's diseases. Given its relative safety, further research is warranted to evaluate the potential of CoQ10 in patients with Alzheimer's disease.

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