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No Effect of Coenzyme Q10 on Cognitive Function, Psychological Symptoms, and Health-related Outcomes in Schizophrenia and Schizoaffective Disorder

Results of a Randomized, Placebo-Controlled Trial

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Abstract:

Background: Cognitive impairments, negative symptoms, affective symptoms, and low energy are highly prevalent features of schizophrenia. Mitochondrial dysfunction has been hypothesized as one of the numerous factors to underlie the manifestation of these symptoms. The objective of this study was to evaluate whether Coenzyme Q10 (CoQ10) has a role in the treatment of schizophrenia and schizoaffective disorder.

Methods: A double-blind, randomized, placebo-controlled trial was conducted to assess the effects of CoQ10 supplementation (300 mg/day) on the coprimary outcomes of attention and working memory performance after 3 and 6 months. Secondary outcomes included plasma CoQ10 levels, mitochondrial function, energy, depression, anxiety, negative symptoms, and quality of life.

Findings: In total, 72 patients were randomized to intervention groups. Overall, there was no effect of CoQ10 supplementation on the primary outcome measures at 3 or 6 months. Further, with the exception of plasma CoQ10 levels, CoQ10 supplementation also had no effect on the secondary outcomes. At 3 months, CoQ10 concentration was significantly higher in the CoQ10 group (3.85 μg/mL) compared with placebo (1.13 μg/mL); this difference was not present at 6 months.

Conclusions: The results of the study suggest that CoQ10 supplementation at 300 mg/day for 6 months is unlikely to be beneficial for cognitive, psychological and health-related outcomes in schizophrenia and schizoaffective disorder. However, a number of limitations including low adherence, modest sample size, and attrition, likely reduce estimates of effects. As such, results should be considered preliminary.

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Y.F. sat on advisory groups for BMS, Janssen, Lundbeck. For the remaining authors none were declared.

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Schizophrenia is a complex, heterogeneous, neurodevelopmental disorder in which cognitive impairments, negative symptoms, symptoms of depression and anxiety, fatigue, and pain are prevalent.[1–4] Cognitive impairments in particular are strongly associated with functional and psychosocial outcomes, as well as ability to engage with psychological interventions.[5–7] As such, interventions, which may target any one or a selection of these interrelated symptoms, are of considerable value.[8]

There is nascent evidence that disrupted bioenergetics and mitochondrial dysfunction contribute to the manifestation of the cognitive impairments, fatigue, affective, and negative symptoms in schizophrenia.[9–11] However, the exact mechanisms responsible for such dysfunction remain elusive. Coenzyme Q10 (CoQ10) is an endogenous compound that is essential for energy production within the mitochondria. To date, 2 small studies have examined levels of CoQ10 in schizophrenia, with conflicting results.[12,13] The first cross-sectional study reported lower levels of CoQ10 in erythrocytes in patients with schizophrenia compared with healthy controls, although no between group difference in plasma concentration was observed.[12] The subsequent study observed lower serum CoQ10 concentration in patients compared with controls; however, on average, patient samples were within normal reference range.[13]

Considering the role of mitochondrial dysfunction in the pathophysiology of schizophrenia, CoQ10 presents as a potential treatment opportunity.[14] CoQ10 supplementation may have beneficial cognitive and clinical effects for patients with schizophrenia through improving mitochondrial function via the restoration of ATP generation and increasing anti-oxidant capacity.[15] The CoQ10 supplementation has been investigated as a single or adjunctive therapy in several neurological and neuropsychiatric disorders for a range of outcomes associated with mitochondrial function, including cognitive function, fatigue, functional capacity, and psychological symptoms.[14] Further, mitochondrial diseases are often treated with CoQ10 as a single therapy or in combination with other mitochondrial agents and antioxidants. The current study aimed to determine the effects of CoQ10 supplementation in patients with schizophrenia or schizoaffective disorder over 3 and 6 months. To this end, a prospective, double blind, randomized placebo controlled trial (RCT) was conducted. Primary outcome measures were difference in attention and working memory performance between CoQ10 and placebo treated

groups at 3 and 6 months. Secondary outcome measures were between group differences in plasma CoQ10 levels, mitochondrial function (lactate),[16] processing speed, executive function, general cognitive function, energy, depression, anxiety, negative symptoms, quality of life, functional status, physical activity, and blood pressure at 3 and 6 months. The study was registered on clinicaltrials.gov [identifier: NCT03576911].

MATERIALS AND METHODS

Design

This RCT compared neuropsychological performance and clinical symptoms of CoQ10 supplemented patients with schizophrenia and schizoaffective disorder to patients who received placebo. Ethical approval for this study was granted by St James' Hospital/Tallaght University Hospital and Newcastle Hospital research ethics committees in Ireland. This study was carried out according to the principles of the Declaration of Helsinki (Amendment 2008) and ICH Good Clinical Practice guidelines—ICH E6 (R2). All patients signed informed consent upon enrolment to the study.

Intervention

Coenzyme Q10 was delivered in soft gelatine capsules containing 100 mg of ubiquinone-10 (CoQ10). The ubiquinone content was taken as valid from the manufacturer and was not independently verified. Placebo capsules were identical in appearance and contained the same nonactive ingredients. The selected daily dose of CoQ10 for this study was 300 mg, divided into three 100-mg doses to be taken with food. The CoQ10 dose was selected following a literature review; 300 mg per day was found to be effective for a variety of symptoms, including pain, depression, and fatigue, with minimal adverse effects.[14] Participants received a 3-month supply of capsules (270 capsules) after their baseline and a 3-month assessment. Adherence to intervention was measured using pill count and patient self-report at follow-up; at 6 months, 61% of participants reported complete adherence to the intervention (<10% of capsules remaining). The researchers also maintained regular contact with patients to promote adherence.

Participants

Adults with a clinical diagnosis of schizophrenia or schizoaffective disorder were recruited to the study from mental health outpatient clinics and day support services. Diagnosis was confirmed by the patient's treating clinician and chart review, or a Structured Clinical Interview for DSM-IV. Along with a clinical diagnosis of schizophrenia or schizoaffective disorder, the inclusion criteria required participants to be aged between 18 and 70 years on entry to the study. Exclusion criteria were a history of seizures, comorbid substance abuse or psychiatric diagnosis in the preceding 6 months, currently pregnant or breastfeeding, previous head injury with loss of consciousness (>3 minutes), uncontrolled thyroid dysfunction, and taking warfarin or another anti-coagulant.

Outcome Assessment

Participants completed a neuropsychological and clinical assessment at baseline, 3 months postrandomization (midpoint), and 6 months postrandomization (endpoint) to evaluate differences between CoQ10 and placebo groups at each time point. Outcome assessments were conducted by a doctoral research student and a clinical research nurse.

Primary Outcome Measures

Sustained attention performance was measured with the Continuous Performance Task—Identical Pairs (CPT-IP).[17] Working memory performance was measured with 2 measures: the between-errors score of Spatial Working Memory (SWM) task from the Cambridge Neuropsychological Test Automated Battery[18] and scaled score on the Letter number sequencing subscale from the Wechsler Memory Scale, 3rd Edition.[19]

Secondary Outcome Measures

The measures and methods used to determine plasma CoQ10 levels, mitochondrial function (lactate), processing speed, executive function, general cognitive function, energy, depression, anxiety, negative symptoms, quality of life, functional status, physical activity, and blood pressure are listed in Table S1 (http://links.lww.com/JCP/A705).

Randomization, Blinding, and Concealment

Upon completing the baseline assessment and confirmation that participation was not contraindicated, participants were randomized to receive CoQ10 or placebo capsules during the study. Randomization was conducted by a research pharmacist at the Clinical Research Facility, St James' Hospital Dublin, using a randomization table stratified by blocks according to age and sex (men aged 18–39 years, women aged 18–39 years, men aged 40+ years, and women aged 40+ years). The randomization table was created by an independent statistician. Study personnel, clinical teams, and participants did not observe the randomization table before or during the course of the study and remained blinded to treatment group allocation throughout the study and outcome assessment. Packaging and gel capsules were visually identical for placebo and CoQ10 to maintain concealment.

Statistical Analysis

Statistical package SPSS 25 for Windows was used. Mean differences between groups on the primary and secondary outcome measures were analyzed using analyses of covariance with treatment group as the independent variable and each outcome variables as the dependent variable. Baseline score on each outcome measure acted as a covariate. Separate analyses were conducted for each follow-up (3 and 6 months postrandomization). The study aimed to recruit 300 participants. Required sample size was calculated based on the primary outcomes and assumption of a moderate treatment effect and approximately 20% attrition rate. We selected 80% power, and a type 1 error rate of 5%. The sample size calculation for the first primary outcome of attention indicated that 69 participants per treatment group would be required, assuming standard deviation (SD) of 0.96. For the second primary outcome of working memory, a total sample size of 250 participants were required, based on the above assumptions, changing SD to 1.3 for standardized scores on SWM. Values used for SD were obtained from previous work within the cohort.[20] Participant attrition resulted in a high volume of missing data. Therefore, the primary analysis reported includes complete cases only, and sensitivity analysis was conducted using the ITT sample, with missing values replaced using multiple imputation.

RESULTS

Seventy-two patients were recruited and randomized into the study, as illustrated in the CONSORT diagram (Supplemental Fig. 1, http://links.lww.com/JCP/A706). The actual sample size was less than the planned. Enrolment rates were lower than anticipated,

and because pragmatic reasons recruitment was stopped. Eligible participants were recruited from November 2016–March 2019.

Baseline Sociodemographic and Clinical Characteristics

Baseline sociodemographic and clinical characteristics of participants are presented for each group in Table S2 (http://links.lww.com/JCP/A707). All participants were taking at least 1 antipsychotic medication upon enrolment into the study; 19.4% were prescribed both oral and long acting antipsychotics and 12.5% were prescribed long-acting antipsychotics only. Atypical antipsychotics clozapine (36.1%), olanzapine (33.3%), and aripiprazole (22.2%) were most frequently prescribed.

Scores on cognitive, biochemical, psychological, and health-related outcome measures at baseline are presented for each group in Table S3 (http://links.lww.com/JCP/A708). Following the CONSORT 2010 statement, significance tests to compare baseline characteristics between randomized groups are not reported.[21] Baseline plasma CoQ10 concentration was not correlated with any other variable at baseline.

Outcome Assessment

After controlling for baseline performance scores, there were no statistically significant differences in mean scores at 3 and 6 months on the attention (CPT-IP) or working memory tasks (SWM Between-errors and LNS) between treatment groups (Table 1). The change in attention and working memory performance scores from baseline at each study visit is shown in Figure 1.

The CoQ10 group showed significantly higher plasma CoQ10 levels at 3 months (estimated marginal mean 3.85 μg/mL for the CoQ10 group vs 1.13 μg/mL for the placebo group, $P < 0.001$). The mean difference between groups (1.45 μg/mL) remained statistically significant within the intention to treat (ITT) sensitivity analysis using multiple imputations, $P = 0.012$. There was no difference in plasma CoQ10 concentration at 6 months (Table 1).

The CoQ10 group performed significantly poorer than the placebo group on the executive function measure SWM Strategy at both time points. However, the difference was not statistically significant within the ITT sensitivity analysis at 3 months (mean difference = 0.67, $P = 0.128$) or at 6 months (mean difference = 0.66, $P = 0.185$). There were no other statistically significant differences between treatment groups at either time point for the remaining outcomes, including mitochondrial function as measured by plasma lactate levels (Table S4, http://links.lww.com/JCP/A709).

Adverse Events

Suspected adverse events occurred in 4 participants. These participants withdrew from the study. In the CoQ10 group, 1 participant reported nausea and 1 reported joint pain. In the placebo group, 1 participant reported nausea and 1 reported light headedness.

DISCUSSION

To our knowledge, this is the first RCT of CoQ10 supplementation in schizophrenia. This preliminary investigation found no evidence that CoQ10 supplementation (300 mg/day) improved cognitive, psychological, or health-related outcomes. However, results need to be interpreted against a background of longer term treatment non-adherence and low participant retention. Although an increase in plasma CoQ10 concentration at 3 months in the CoQ10 group compared with placebo was observed, demonstrating treatment adherence at that point—a comparative plasma increase was not evident at 6 month analysis.

Critically, given that plasma CoQ10 status at 6 months was no longer significant between the 2 treatment groups, it is probable

TABLE 1. Mean Difference Between Groups at 3-Month Follow Up (Midpoint) and 6-Month Follow Up (Endpoint) on the Primary Outcome Measures for Attention and Working Memory, and the Secondary Outcome Measure Plasma CoQ10

	3-Month Follow-up					6-Month Follow-up				
	Descriptive Statistics		Difference Between Groups			Descriptive Statistics		Difference Between Groups		
	Placebo Mean (SE)	CoQ10 Mean (SE)	Mean difference (95% CI)	*F*	*P*	*Placebo Mean(SE)*	*CoQ10 Mean(SE)*	*Mean difference (95% CI)*	*F*	*P*
Primary outcome measure										
Attention										
CPT-IP: 2 digits	3.07 (0.15)	2.66 (0.15)	0.41 (−0.1 to 0.84)	3.83	0.057	2.97 (0.15)	2.95 (0.16)	0.02 (−0.43 to 0.47)	0.01	0.942
CPT-IP: 3 digits	1.91 (0.14)	2.24 (0.15)	−0.33 (−0.75 to 0.10)	2.42	0.127	2.51 (0.17)	2.25 (0.18)	0.26 (−0.24 to 0.76)	1.13	0.294
CPT-IP: 4 digits	1.21 (0.12)	1.14 (0.12)	0.07 (−0.28 to 0.42)	0.17	0.685	1.25 (0.15)	1.46 (0.16)	−0.21 (−0.65 to 0.23)	0.96	0.333
Working memory										
SWM (Errors)	−1.22 (0.18)	−1.48 (0.18)	0.26 (−0.26 to 0.77)	1.01	0.321	−1.07 (0.17)	−1.24 (0.18)	0.17 (−0.33 to 0.67)	0.46	0.499
Letter number sequencing	8.96 (0.60)	8.24 (0.64)	0.72 (−1.07 to 2.50)	0.65	0.424	8.76 (0.64)	8.75 (0.68)	0.02 (−1.88 to 1.80)	0.00	0.988
Secondary outcome measure										
Plasma CoQ10 (μg/mL)	1.31 (0.49)	4.46 (0.56)	−3.15 (−4.67 to −1.62)	17.83	<0.001	1.25 (0.31)	2.05 (0.37)	−0.80 (−1.78 to 0.18)	2.77	0.107

Estimated marginal mean, standard error (SE), mean difference, and 95% confidence interval of mean difference between groups adjusted for baseline task performance score are presented,

95% CI, 95% confidence interval.

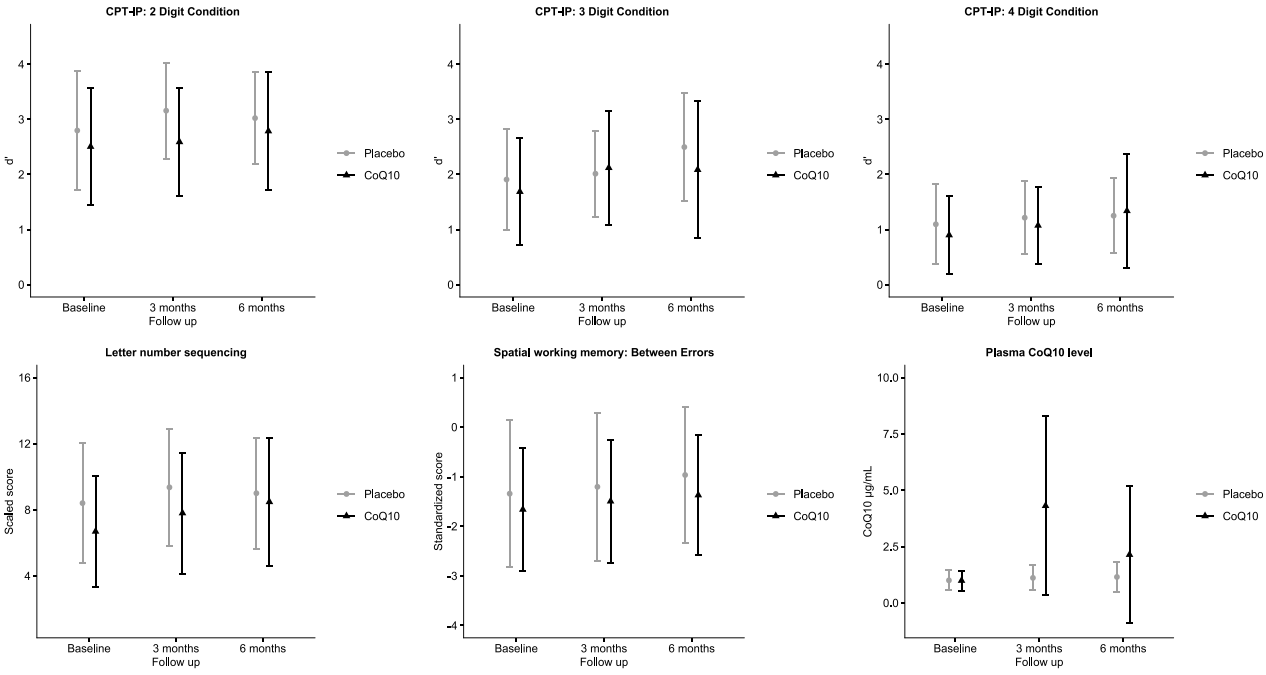

FIGURE 1. Attention and working memory performance, and plasma CoQ10 arithmetic means and standard deviation at baseline, 3-month and 6-month follow-up. Follow-up values presented in the figure are not adjusted for baseline. All detected CoQ10 values were included in the calculations. No samples were found to have zero CoQ10 levels.

that treatment non-adherence is a principal confounding factor to the negative outcomes. Although intra-individual variability may account for some discrepancies, it is likely that participants became less treatment adherent as the study progressed, given that 61% of completing participants indicated full adherence at 6 months. Further, pill count and patient self-report can be inaccurate indications of adherence, as they are both subject to social desirability and response biases.[22] Deviations from the treatment regime, such as taking more than 1 capsule at a time or without food, which would influence CoQ10 absorption, were not recorded. Thus, in some cases adherence to assigned intervention may have been over-estimated. Immediacy of treatment response and belief in medication effects are predictors of adherence behavior in schizophrenia and enduring mental illness.[23,24] The absence of statistically significant treatment effect within the sample may be both a cause and consequence of adherence behavior. Nonetheless, non-adherence to treatment is a frequent occurrence in outpatient populations with schizophrenia and other enduring mental illnesses. As such, although power to detect a significant effect may be greatly reduced due to increased and artificial variability, the overall findings may be more generalizable to routine care.

There is nascent evidence that mitochondrial dysfunction is present in patients with schizophrenia and schizoaffective disorder, and this dysfunction is one of numerous factors implicated in the manifestation of cognitive impairment and clinical symptoms. We anticipated that CoQ10 supplementation would have beneficial cognitive and clinical effects for patients with schizophrenia through improving mitochondrial function via the restoration of ATP generation and increasing antioxidant capacity.[15] Yet there appeared to be no effect of CoQ10 supplementation (300 mg/day) on cognition, energy, psychological symptoms, quality of life, functional status, physical activity and blood pressure. Importantly we also found no effect on plasma lactate level, which was used as a marker for mitochondrial function.[16] One possible reason for this is that a deficit in CoQ10 was not present in the majority of participants who took part in the study. Further, baseline plasma CoQ10 concentration was not correlated with any other variable at baseline, including plasma lactate concentration.[16] It is possible that only patients who exhibit CoQ10 deficiency will benefit clinically from supplementation, as exogenous CoQ10 may be able to replenish a deficit in CoQ10 status and result in some degree of improvement in ETC function.[25] Schizophrenia is a highly heterogeneous condition, and a subgroup of participants who exhibit greater mitochondrial dysfunction and CoQ10 deficits may exist. Identifying and evaluating the effects of CoQ10 in such a subgroup may be warranted.

A major limitation of the CoQ10 RCT is the limited sample size as a result of recruitment and retention difficulties. To detect a moderate treatment effect on the primary outcomes, 250 participants needed to be randomized to and complete the intervention. As a result, the CoQ10 RCT did not have sufficient power to detect the anticipated moderate effect of CoQ10 on the primary outcomes of attention and working memory. Additionally, there was a large attrition rate of 34% from the study by 6 months; further reducing power to detect an effect of CoQ10.

Finally, the level of plasma CoQ10 remained below 4.32 µg/mL at all times in the current study. This level has been reported to elicit biochemical improvement in cell models of mitochondrial diseases,[25] as such a higher dose may have elicited different results. Further studies using higher doses of CoQ10 may be warranted to confirm or refute the results of this study; however consideration must be given to the feasibility of conducting higher dose studies, with evidence of low treatment adherence within this study.

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