Evaluating the Effect of Coenzyme Q10 Augmentation on Treatment of Bipolar Depression

A Double-Blind Controlled Clinical Trial

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Abstract:

Background: Bipolar disorder (BPD) is a chronic and recurrent mood disorder characterized by episodes of mania, hypomania, and major depression. Based on available evidence, mitochondrial dysfunction, oxidative stress, and inflammation have important roles in the pathophysiology of bipolar depression. More specifically, it seems that coenzyme Q10 (CoQ10), a mitochondrial modulator, as well as an antioxidant and anti-inflammatory agent, might be effective in modulating these pathophysiological pathways. Accordingly, the aim of this study was to investigate whether and to what extent, compared with placebo, adjuvant CoQ10 might improve symptoms of depression in patients with BPD.

Methods: A total of 69 patients with BPD with a current depressive episode were randomly assigned either to the adjuvant CoQ10 (200 mg/d) or to the placebo group. Standard medication consisting of mood stabilizers and antidepressants was consistent 2 months prior and during the study. Depression severity for each patient was assessed based on the Montgomery-Asberg Depression Rating Scale scores at baseline, fourth week, and eighth week of the study.

Results: Symptoms of depression decreased over time in both groups. Compared with the placebo group, adjuvant CoQ10 to a standard medication improved symptoms of depression after 8 weeks of treatment. In addition, at the end of the study, it turned out that more responders were observed in the CoQ10 group, compared with the placebo group. CoQ10 had minimal adverse effects and was well tolerated.

Conclusions: The present pattern of results suggests that among patients with BPD, compared with placebo, adjuvant CoQ10 probably because of its antioxidant and anti-inflammatory properties can improve symptoms of depression over a period of 8 weeks.

Key Words: bipolar depression, coenzyme Q10, mitochondrial dysfunction, oxidative stress

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It is estimated that up to 1.2% of the general population have bipolar disorders (BPD).[1,2] Typically, people with BPD report chronic and recurrent fluctuations of mood and energy, marked by episodes of mania, hypomania, and major depression.[3] There are many reasons indicating the importance of depressive episodes of BPD, which include the following: majority of patients with BPD mostly represent subthreshold depression and they experience residual depressive symptoms or hypomanic symptoms between attacks, and they often seek treatment during their depressive episodes.[4,5] Presenting a depressive episode at disease onset is associated with poor prognosis. In addition, the depression phase of BPD is accompanied by higher risk of suicide and function impairment.[6]

Despite the clinical significance of bipolar depression and its deteriorative impact on quality of life of these patients, conventional treatments of bipolar depression are limited and have not been studied broadly, and treatment of depressive symptoms is more difficult than in the manic phase. In addition, proper treatment, in addition to targeting acute depressive symptoms, is needed to prevent switching of phase.[7]

The biological and psychological etiologies of BPD are not completely understood. Although it is estimated that heritability might be up to 85%, a multifactorial model of gene-environment interaction is believed to best fit this disorder.[1,2,8,9] Most importantly, it appears that changes at neural levels such as hyperexcitability, mitochondrial dysfunction, dentritic spine loss, altered membrane permeability, and endoplasmic reticulum stress might cause changes at the level of circuitry and brain matter, such as grey matter loss and default-mode network deactivation failure, which ultimately impacts negatively on systemic consequences such as allostatic load, metabolic syndrome, oxidative stress, and inflammation.[8–10]

In the search of further psychopharmacologic treatment options beyond mood stabilizers, antipsychotics, and antidepressants, recent research has focused on the role of mitochondrial dysfunction in the pathophysiology of BPD.[11–14] Mitochondria is a cell organelle playing an important role in energy production (in the form of adenosine triphosphate through oxidative phosphorylation pathway).[15] As the brain requires more energy than other parts of the body to maintain its normal function, the energy metabolism defect in the brain results in neuroprogression and cognitive disorders, which are common among patients with BPD.[16,17]Abnormal cellular energy production, phospholipid metabolism, and impaired electron transfer chain can lead to overproduction of reactive oxygen species and oxidative stress. Furthermore, inflammatory cytokines play an important role in pathology of BPD.[10,18–20] Therefore, agents with mitochondrial modulating effects and antioxidant and anti-inflammatory properties such as coenzyme Q10 (CoQ10) can be considered as potential treatments for BPD.[21]

CoQ10 is an endogenous lipid-soluble antioxidant that can provide defense against cell damage by decreasing oxidative stress and inflammatory responses.[22–25] A wide variety of roles are attributed to CoQ10 including regulation of cell metabolism and inflammation by means of regulating gene expression and reducing the serum level of oxidative stress biomarkers. It is also an important part of electron transfer chain in mitochondria. Diminished serum level of CoQ10 is associated with multiple diseases such as cardiac, skeletal, and neurologic diseases.[26] Interestingly, there

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is some evidence supporting the beneficial effects of CoQ10 in the treatment of neurodegenerative disorders such as Huntington and Parkinson diseases.[27,28] In addition, lower serum level of CoQ10 have been observed in patients with depression,[26] and preliminary evidence has demonstrated antidepressant effects of CoQ10 in animal and human studies.[28,29] Therefore, considering the role of mitochondrial dysfunction, inflammation, and oxidative stress in the pathophysiology of bipolar depression and the antioxidant, anti-inflammatory, and mitochondrial modulatory properties of CoQ10, it may exert beneficial effects in the treatment of bipolar depression. Hence, the aim of present study was to evaluate the effects of CoQ10 as adjuvant treatment of the depressive phase of BPD.

METHODS

Procedure

Eligible outpatients with BPD and with current depressive episode were evaluated to be enrolled in this study. All participants were informed about the study protocol and aims, and gave their written informed consent. After a thorough psychiatric and medical interview, patients were randomly assigned either to the placebo or to the adjuvant CoQ10 group. Experts blind to the patients' study assignment used the Montgomery-Asberg Depression Rating Scale (MADRS) to rate patients' symptoms of depression at baseline and after 4 and 8 weeks (end of the study). The entire study was performed from December 2016 to November 2017 in an outpatient psychiatry clinic affiliated with Hamadan University of Medical Sciences in Hamadan (Iran). The local ethics committee approved the study, which was performed in accordance with the rules laid down in the Declaration of Helsinki and its later amendments. The study was registered in the Iranian Registry of Clinical Trials (IRCT2016092622965N4).

Sample

Patients were included in this study if the following inclusion criteria were met at the baseline of the study: (a) based on a psychiatric interview [Mini International Neuropsychiatric Interview (MINI)[30]], a psychiatrist or clinical psychologist diagnosed a BPD, currently a depressive episode based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; (b) age

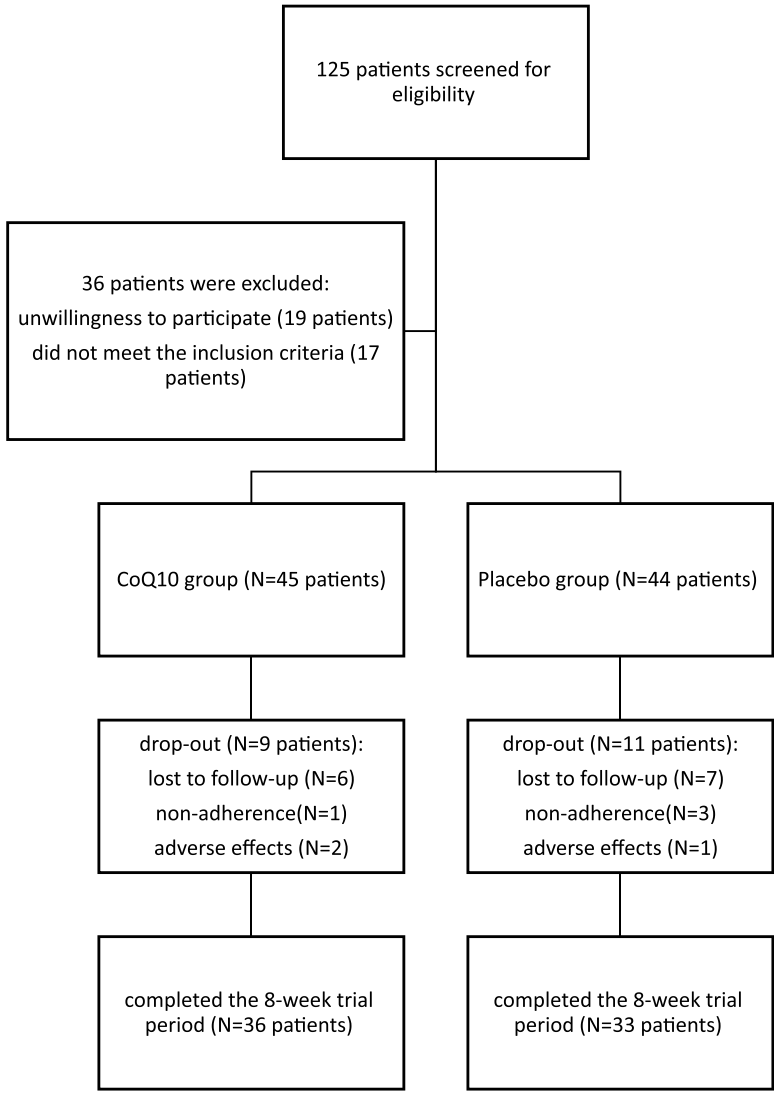

FIGURE 1. Study flow diagram.

between 18 and 65 years; (c) MADRS score above 15 points (mild to severe depression); and (d) individual medication regimen at least 2 months before the study begin and throughout the 8 weeks of the study. Exclusion criteria of the study were as follows: (a) patients with mixed episodes; (b) comorbid psychiatric disorders such as anxiety disorder, schizophrenia, current state of psychosis, and substance use disorder; (c) pregnancy or lactation, or expecting to get pregnant during the treatment; (d) poor adherence to the treatment (using the medication for less than 80% of study period); (e) presence of any adverse effects resulting in patients' intolerance or complications; and (f) unwilling or unable to follow the study protocol.

Sample Size Calculation

The software g*power®[31] was used. A total sample size of 37 patients in each group was calculated on the basis of the expected changes on MADRS (as primary outcome measure), considering $\alpha = 5\%$, a power of 90%, and 10% dropout.

As shown in the flowchart (Fig. 1), 125 patients were screened for recruitment. Among these, 17 patients did not meet the inclusion criteria, and 19 patients did not agree to participate in the study. The remaining 89 patients were randomly allocated into 2 groups to receive either CoQ10 or placebo.

Randomization

To achieve random group assignment, a computer-generated random-number sequence was prepared in advance and sealed in opaque, consecutively numbered envelopes by a researcher not further involved in the study. Group sampling occurred blockwise. Patients were blind to the study allocation; they were assigned either to the adjuvant CoQ10 or to the placebo group. Once an envelope was drawn, it was put aside and not returned to the ballot box again.

Intervention and Placebo Groups

All patients kept their individual medication regimen stable 2 months before entering the study and during the entire study lasting 8 weeks. Patients in the CoQ10 group were instructed to use 200 mg/d (Bonyad Salamat Kasra, Tehran, Iran), whereas patients in the placebo group were instructed on how to use the placebo tablets. CoQ10 and placebo were identical in shape, color, scent, and consistency. The psychologist responsible for medication was not further involved in the study.

Assessing Adverse Effects

To assess adverse effects of CoQ10 and placebo administration, all patients were asked at every time point whether they had experienced one or more of the following possible adverse effects (the list was based on the Joint Formulary Committee[32]; answers: yes/no). The numbers in [squared brackets] are frequencies of "yes" responses for the adjuvant CoQ10 and placebo: rash, drowsiness, anxiety, dizziness, headache, insomnia, agitation and/or hallucinations, vomiting, light-headedness, vertigo, weakness, chest pain and peripheral edema, constipation, diarrhea, dyspepsia, flatulence, nausea, flu-like syndrome, allergic reaction, arthralgia,

TABLE 1. Overview of the Descriptive and Inferential Statistical Indices of Sociodemographic, Illness-, and Medication-Related Characteristics at Baseline and Separately for Patients Treated With Adjuvant CoQ10 or Placebo

Variable	Groups		Statistics
	CoQ10 (n = 36)	Placebo (n = 33)	
	Mean (SD)	Mean (SD)	
Age, y	37.47 (10.69)	39.52 (10.82)	$t(67) = 0.79$, $P = 0.43$
Age at disease onset, y	24.52 (15.41)	21.87 (2.38)	$t(67) = 0.90$, $P = 0.34$
Duration of bipolar disorders, y	12.95 (13.34)	17.65 (12.32)	$t(67) = 1.10$, $P = 0.29$
Duration of current depressive episode, mo	2.20 (1.12)	2.06 (0.86)	$t(67) = 0.66$, $P = 0.51$
	n/n	n/n	
Sex (male/female)	8/28	3/30	$\chi^2(N = 69, df = 1) = 2.22$, $P = 0.19$
Marital status (single/married/divorced)	14/18/4	9/21/3	$\chi^2(N = 69, df = 2) = 1.33$, $P = 0.52$
Education (illiterate/primary/high school diploma/academic)	3/10/11/12	3/9/10/11	$\chi^2(N = 69, df = 3) = 0.01$, $P = 0.99$
Occupation (unemployed/housewife/employee/self-employment)	9/18/6/3	5/25/3/0	$\chi^2(N = 69, df = 3) = 6.14$, $P = 0.10$
Place of residence (no.; urban/rural)	27/6	32/4	$\chi^2(N = 69, df = 1) = 0.65$, $P = 0.45$
Somatic comorbidity and concomitant medications (yes/no)	3/30	1/35	$\chi^2(N = 69, df = 1) = 1.26$, $P = 0.26$
Conventional medications for bipolar depression (yes/no)			
Olanzapine	15/21	15/18	$\chi^2(N = 69, df = 1) = 0.10$, $P = 0.75$
Quetiapine	2/34	0/33	$\chi^2(N = 69, df = 1) = 1.89$, $P = 0.17$
Lithium carbonate	4/32	1/32	$\chi^2(N = 69, df = 1) = 1.67$, $P = 0.19$
Sodium valproate	2/34	0/33	$\chi^2(N = 69, df = 1) = 189$, $P = 0.17$
Clonazepam	13/23	13/20	$\chi^2(N = 69, df = 1) = 0.08$, $P = 0.78$
Sertraline	23/13	24/9	$\chi^2(N = 69, df = 1) = 0.62$, $P = 0.43$
Citalopram	3/33	4/29	$\chi^2(N = 69, df = 1) = 0.27$, $P = 0.60$
Adverse effects (yes/no)			
Epigastric issues	4/32	2/31	$\chi^2(N = 69, df = 1) = 1.26$, $P = 0.26$
Dizziness	1/35	3/30	$\chi^2(N = 69, df = 1) = 1.26$, $P = 0.26$
Sleep impairments	5/31	3/30	$\chi^2(N = 69, df = 1) = 1.09$, $P = 0.34$

TABLE 2. Overview of Descriptive and Inferential Statistical Indices of the MADRS Scores, Separately for the 3 Time Points (Baseline, Week 4, and Week 8), and for the 2 Groups (Adjuvant CoQ10 vs Placebo)

	Time Points			Statistics
	Baseline	Week 4	Week 8	Greenhouse-Geisser epsilon (ε): .738
	Mean (SD)	Mean (SD)	Mean (SD)	Time: $F(2,134) = 229.98$*** .774 [L]
Adjuvant CoQ10 (n = 36)	23.92 (5.15)	14.78 (3.92)	11.08 (3.05)	Group: $F(1,67) = 0.79$ .012 [S]
Placebo (n = 33)	21.64 (6.60)	16.22 (4.92)	14.55 (4.75)	Time × group interaction: $F(2,134) = 18.57$*** .217 [L]

***$P < 0.001$.

[S] indicates small effect size; [L], large effect size.

myalgia, back pain, arthritis, urinary tract infection, sinusitis, pharyngitis, bronchitis, and rhinitis (see Table 1 for results).

Assessment of Depressive Symptoms

Experts rated patients' symptoms of depression with the Persian version of MADRS. The questionnaire consists of 10 items, and answers are given on a 7-point rating scale ranging from 0 to 6. Total score ranges from 0 to 60, with higher scores reflecting more severe symptoms of depression. Furthermore, the following categories are reported: normal or remission (0–6), mild depression (7–19), moderate depression (20–34), and severe depression (>34).Validity and reliability of this questionnaire were confirmed in the Iranian population by Ahmadpanah et al .[33] At baseline, week 4, and week 8, subjects were assessed for their depression severity based on the MADRS.

Required demographic characteristics of patients (age, sex, marital status, education, occupation, and place of residence), comorbidities, and concomitant medications were recorded. In addition, patients were regularly asked about the presence of any adverse effect whatsoever.

Statistical Analysis

All statistical computations were performed per protocol. Comparisons between the 2 groups (adjuvant CoQ10 and placebo) of sociodemographic, illness- and treatment-related information were performed with t and χ^2 tests. Next, an analysis of variance (ANOVA) for repeated measures with the factors time (baseline, week 4, and week 8), group (adjuvant CoQ10 and placebo), and the time × group interaction, and MADRS scores as dependent variable was performed. Because of the deviation from sphericity, the ANOVA was performed using Greenhouse-Geisser–corrected degrees of freedom, although the original degrees of freedom are reported with the relevant Greenhouse-Geisser epsilon value (ε). For the ANOVA, effect sizes were indicated with the partial eta squared (η_p^2), with $0.01 \leq \eta_p^2 \leq 0.059$ indicating small [S], $0.06 \leq \eta_p^2 \leq 0.139$ indicating medium [M], and $\eta_p^2 \geq 0.14$ indicating large effect sizes [L]. To compare MADRS scores within the 2 groups for the 3 time points, and between the 2 groups for the 3 time points, we followed Becker[34] and listed the effect sizes (Cohen d) for synthesizing standard mean measures. Following Cohen,[35] effect sizes were reported as follows: $d < .49$, small effect size [S]; $.50 < d < .79$, medium effect size [M]; $d > .80$, large effect size [L].

Last, to calculate the odds to be a responder (improvement of MADRS scores of 50% or more) and a remitter (MADRS ≤7) in the CoQ10 group, compared with the placebo group, 2 odds ratio (OR) calculations were performed.

The level of significance was set at $P \leq 0.05$, and all statistics were processed using SPSS 25.0 (IBM Corp, Armonk, NY) for Apple McIntosh.

TABLE 3. Overview of Effect Size Calculations Within the 2 Study Conditions (Adjuvant CoQ10 and Placebo) and for the 3 Time Points

	Groups	
	CoQ10	Placebo
Baseline–week 4	1.99 [L]	0.92 [L]
Baseline–week 8	3.04 [L]	1.23 [L]
Week 4–week 8	1.05 [L]	0.39 [S]

[S] indicates small effect size; [L], large effect size.

RESULTS

Sample Characteristics

The study flow diagram is shown in Figure 1. Of the 89 patients who were randomized to participate in the study, 7 patients were excluded due to nonadherence secondary to patient unwillingness to continue the medication or experiencing intolerable adverse effects, and 13 patients were excluded because of loss to follow-up.

Table 1 shows the sociodemographic, illness-, and medication-related information of the adjuvant CoQ10 and the placebo group. No statistical significant differences were observed between the 2 groups as regard sociodemographic, illness-, and medication-related information.

MADRS Scores, Between and Within the 2 Groups and Over Time

Table 2 shows the descriptive and inferential statistical overview of the MADRS scores for the 2 groups and over time.

The MADRS scores decreased statistically significantly over time. The MADRS scores did not differ between the 2 groups. The statistically significant time × group interaction showed that the MADRS scores did decrease over time, but more so in the CoQ10 group, compared with the placebo group.

TABLE 4. Overview of Effect Size Calculations Between the 2 Study Conditions (Adjuvant CoQ10 and Placebo) and for the 3 Time Points

	Time Points		
	Baseline	Week 4	Week 8
Adjuvant CoQ10 vs placebo	0.38 [S]	0.34 [S]	0.87 [L]

[S] indicates small effect size; [L], large effect size.

TABLE 5. Response and Remission Rates at the End of the Study for the CoQ10 and the Placebo Condition

		Group		
		CoQ10	Placebo	Statistics
No.		36	33	
Response	Yes	26	4	χ^2(N = 69, *df* = 1) = 25.31, *P* = 0.001
	No	10	29	
Remission	Yes	3	0	χ^2(N = 69, *df* = 1) = 2.88, *P* = 0.09
	No	33	33	

Single Mean Comparisons

Tables 3 and 4 summarize the single mean comparisons (effect sizes) within the 2 groups and between the 2 groups.

In the QoQ10 group, the MADRS scores decreased significantly from baseline to week 4, from baseline to week 8, and from week 4 to week 8 (always large effect sizes).

In the placebo group, the MADRS scores decreased significantly from baseline to week 4 and from baseline to week 8 (always large effect sizes), but not from week 4 to week 8 (small effect size).

As shown in Table 4, between the CoQ10 and placebo groups, effect sizes for mean differences were small at baseline and at week 4, but the effect sizes were large at week 8.

Responders and Remitters

To calculate the odds to be a responder (improvements of 50% or more of the MADRS scores) or a remitter (MADRS ≤7) in the CoQ10 group, compared with the placebo group, 2 OR calculations were performed. Table 5 reports the response and remission rates at the end of the study, separately for the 2 study groups.

As regard the response to the treatment at the end of the study, it turned out that more responders were observed in the CoQ10 group, compared with the placebo group. Accordingly, the odds of being a reponder at the end of the study was 18.85-fold higher in the CoQ10 group, compared with the placebo group [OR, 18.85; confidence interval (CI), 5.27–67.44].

As regard the remission at the end of the study, there was no higher odds of being a remitter in the CoQ10 group, compared with the placebo group (OR, 1.09; CI, 0.99–1.29).

DISCUSSION

The key findings of the present study were that among outpatients with diagnosed BPD and currently in a depressive episode and compared with a placebo group, adjuvant CoQ10 to a standard medication improved symptoms of depression after 8 weeks. The present data add to the current literature in that to our knowledge, this was the first randomized and placebo-controlled clinical trial to show the favorable impact of adjuvant CoQ10, compared with a placebo group.

Following previous and preliminary results,[17,29] we assumed that adjuvant CoQ10 improved symptoms of depression in patients with BPD and currently in a depressive state, compared with placebo, and the data did confirm this (see Tables 2–4, Fig. 2). Importantly, the favorable effect of adjuvant CoQ10 was observable above all also from week 4 to week 8 (large effect size) within the group of adjuvant CoQ10, but also compared with the placebo group at week 8 (Table 4). Accordingly, it appears that administration of adjuvant CoQ10 should last at least for 8 weeks.

The quality of the data does not allow a deeper and, above all, neurophysiological understanding of the underlying mechanisms. For want of direct measurement and assessment, we rely on previous studies.

Evidence showed that in addition to neurotransmitter dysregulation, several other pathophysiologic pathways are also important in the neuropathology of BPD. The roles of mitochondrial dysfunction, alterations in inflammatory cytokines production, and oxidative stress have already been verified in the pathogenesis of bipolar depression.[10,36,37] Confirming the role of inflammation and oxidative stress in the pathophysiology of BPD, several studies reported that conventional treatments of BPD such as atypical antipsychotics, lithium, lamotrigine, and sodium valproate exhibit anti-inflammatory and antioxidant properties. In addition, agents that are able to affect mitochondrial function such as allopurinol have demonstrated beneficial effects on the treatment of BPD.[38–41] Furthermore, in recent years, the efficacy of agents with well-known antioxidant and anti-inflammatory effects including *N*-acetyl cysteine, ascorbic acid, eicosapentaenoic acid, minocycline, and tumor necrosis factor α inhibitors in the treatment of depressive symptoms have been evaluated in several studies.[42–46] Results of these studies showed that agents possessing antioxidant and anti-inflammatory effects can be considered as potential therapeutic options in these patients. In this view, CoQ10 is an essential cofactor for mitochondrial function that exerts potent antioxidant and anti-inflammatory effects. Hence, it has been used in diverse clinical groups, and it has shown beneficial effects in the improvement of disease with mitochondrial dysfunction including heart failure, atherosclerosis, hypertension, hyperlipidemia, diabetes, and male infertility.[47]

Because of neuroprotective effects, CoQ10 has been effective in the treatment of several neurodegenerative diseases such as Parkinson disease, multiple sclerosis, prophylaxis of migraine headaches, and Alzheimer disease.[27,48–51] Recent studies demonstrated that CoQ10 has a possible role in depressive disorders. In a similar

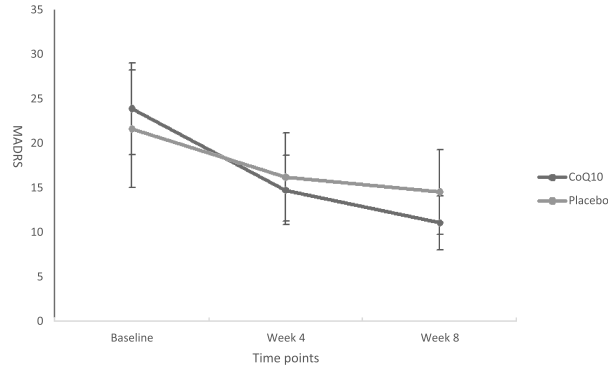

FIGURE 2. The MADRS scores between and within the 2 groups, and over time. Montgomery-Asberg Depression Rating Scale (MADRS) scores decreased over time, but more so in the CoQ10 condition, compared to the control condition. Points are means and bars are standard deviations.

vein, Maes et al[52] showed that plasma CoQ10 level was significantly lower in depressed patients as compared with normal controls.

Next, there are also some studies that support the antidepressant effects of CoQ10. Results of the study by Aboul-Fotouh et al[28] showed antidepressant effects of CoQ10 in an animal model of depression. In addition, in that study, CoQ10 had dose-dependent protective effects against DNA damage and hippocampal oxidative and nitrosative stress.[28] In another study, Forester et al[17,29] evaluated the effects of CoQ10 in the treatment of geriatric bipolar depression. In that study, CoQ10 consumption resulted in significantly reduced depressive symptoms based on MADRS score, although there were no significant differences in creatine kinase activity in the brains of subjects under study. Specific depressive symptoms such as lassitude, sadness, and concentration difficulties did improve significantly, which might be attributed to energy-enhancing properties of CoQ10.[17,29] Although this study was performed in geriatric bipolar depression, results of that study were consistent with our results and demonstrated the potential efficacy of CoQ10 in the treatment of bipolar depression. Despite the use of relatively high CoQ10 doses (between 800 and 1200 mg/d) in these studies, it had excellent tolerability in these patients.

Despite the novelty of the findings, several limitations should warn against overgeneralization. First, we did fully rely on experts' ratings of patients' symptoms of depression. Accordingly, future studies should also assess patients' view of their symptoms. Second, serum levels of CoQ10, oxidative stress, or inflammatory biomarkers were not assessed, which would have allowed a deeper understanding of the underlying neurophysiological changes and probable mechanisms of CoQ10 in the treatment of depression. Third, in this view, it would have been favorable to also assess further and well-established biomarkers such as objective sleep, cortisol, or even brain-derived neurotrophic factor to compare neurophysiological markers with subjective changes of depression. Fourth, it is also conceivable that latent and unassessed physiological and psychological variables might have biased 2 or more dimensions in the same or opposite direction. Last, we kept the CoQ10 dosage stable throughout the entire study, but perhaps higher doses of CoQ10 would have allowed an even more favorable pattern of results.

CONCLUSIONS

In conclusion, considering pathways in pathogenesis of BPD including mitochondrial dysfunction, oxidative stress, and inflammation, it appears that CoQ10 has the potential to be proposed as an effective therapeutic option in the improvement of depressive symptoms of the depression phase of BPD.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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