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Antidepressant effects of open label treatment with Coenzyme Q10 in Geriatric Bipolar Depression

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Introduction

Although bipolar disorder (BD) often presents in young adulthood, most individuals experience recurrent mood episodes, psychosocial deficits and high utilization of health services that persist into later life.¹ Bipolar depression represents the predominant and least successfully treated phase of this illness. Individuals with BD spend more time ill with depressive symptoms than with manic/hypomanic or with cycling/mixed symptoms,²⁻⁴ and the proportion of time spent in depressive episodes to time spent in manic episodes increases with age. The few medications (quetiapine, lurasidone, olanzapine-fluoxetine) FDA-approved for treatment of bipolar depression were studied in predominantly middle-adult-aged cohorts. The clinical management of bipolar disorder in later life is also complicated by medical co-morbidity, cognitive impairment and polypharmacy.⁵ Furthermore, the neurobiological mechanisms that underlie bipolar depression may change with age and resistance to current treatments is high.^{6,7}

Over the past decade there has been increasing evidence⁸ that implicates alterations in bioenergetic metabolism and enhanced oxidative stress in the neurobiology of bipolar disorder.⁹ Although the degree of mitochondrial dysfunction does not produce a substantial systemic metabolic disorder, it is likely sufficient to impact the CNS, as the brain requires twenty-fold the energy production of the rest of the body.⁹ Furthermore, the efficiency of mitochondrial energy production declines with age, an effect seen both in CNS and peripheral tissue. Successful treatment strategies for late life bipolar disorder may depend on developing novel ways to address reduced mitochondrial ATP (adenosine triphosphate) production.

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Coenzyme Q10 (CoQ10) is present in the phospholipid bilayers of mitochondria,¹⁰ shuttling electrons within the mitochondrial electron transport chain to generate ATP and serving as a potent antioxidant.¹¹ CoQ10 has been studied as a treatment for disorders implicating mitochondrial impairment, including congestive heart failure, diabetes, and degenerative neurological conditions.¹²⁻¹⁵ We now present the results from an open-label study of CoQ10 (added to existing treatment at a dosage of 800 mg/day for 4 weeks) for the treatment of older adults with a current episode of bipolar depression. We hypothesized that CoQ10 would reduce depressive symptoms as measured by the Montgomery Asberg Depression Rating Scale (MADRS).

Materials and Methods

Following IRB approval, subjects were recruited to participate in two studies investigating the bioenergetic effects of CoQ10 utilizing a ³¹P-MRS protocol at 4 Tesla (T)¹⁶ (Forester, unpublished). Subjects met DSM-IV TR criteria for Bipolar Disorder, Type I or II, current episode depressed, and were excluded with any previous or current co-morbid Axis I disorder, unstable medical illness, untreated thyroid dysfunction, a history of substance abuse within the past year, Young Mania Rating Scale (YMRS) score of > 6, or Montgomery Asberg Depression Rating Scale (MADRS) < 18. Subjects with bipolar depression continued concomitant psychotropic medication during the study but dosages were left unchanged for the two weeks prior to treatment initiation and during the 4-week study period unless a change in dosage was clinically necessary.

At all study visits (Baseline, Week 2 and 4 of treatment) subjects had a psychiatric interview and completed MADRS and YMRS ratings and drug accountability assessments. Adverse events and vital signs were also recorded. The dosage of CoQ10 was started at 400 mg daily for two weeks and then titrated up to a dosage of 800 mg once daily for weeks 3 and 4. The dose escalation schedule was modified if tolerability issues developed. At the final study visit, CoQ10 was tapered to 400 mg per day for three days and then discontinued and subjects were referred for ongoing clinical treatment.

Multiple degree of freedom comparison of MADRS between baseline and follow-up scores, and single degree of freedom comparisons between baseline and follow-up scores at Weeks 2 and 4, were performed in the presence of an overall association significant at the alpha=0.05 level. Age, sex and statin use were each added separately as co-variables to assess for their individual associations with changes in MADRS ratings. Repeated measures linear regression models were fit using the PROC MIXED routine for SAS statistical software (version 9.1.3). All statistical tests were two-sided and performed at the alpha=0.05 significance level.

Results

Eighty older adults, age 55 and above, were screened and a total of 32 individuals with DSM-IV-TR Bipolar Disorder, Type I or II, current episode depressed (BPD) signed informed consent. Eighteen subjects completed the 4-week trial of CoQ10, nine did not meet inclusion criteria, four withdrew for reasons unrelated to study protocol and 1 withdrew

during the trial due to diarrhea. The sample included 19 participants (18 non-Hispanic white and 1 African American). Ten of the 19 subjects were male, with a mean age of 63 ± 6.54 years (age range 56-78 years). The mean age of onset of bipolar disorder was 26.7 ± 18.0 years (with age of first depressive episode 27 ± 18.2 years and age of first manic episode 34.6 ± 16.9 years). Baseline mood measures indicated moderate depression severity (MADRS score mean 23.89 ± 6.90) and low manic symptom severity (YMRS score mean 4.26 ± 3.68). Concomitant psychotropic medication and mean daily dose by subject is provided in Table 1.

There was a significant reduction in total MADRS score from baseline through Week 4 of the study after co-varying for age, sex and statin use ($F(2,34)=8.09$; $p = 0.001$). A post-hoc analysis of change from baseline to Week 2 was marginally significant ($t_{34} = -1.85$; $p=0.07$), while the change from baseline to week 4 was strongly significant ($t_{34} = -4.02$; $p<0.001$). Furthermore, a secondary exploratory analysis of the change in a three factor symptom domain model of the MADRS¹⁴ indicated a significant decline over 4 weeks in the retardation factor that includes symptoms of lassitude, inability to feel, apparent sadness and concentration difficulties. CoQ10 was well tolerated by study participants. Only one subject discontinued treatment prior to study completion due to an adverse effect (diarrhea developed within three days of initiating treatment with CoQ10 at 400 mg/day and resolved shortly after discontinuation of CoQ10). There were no serious or unexpected adverse events. Other AEs not felt to be related to study medication included a recurrence of atrial fibrillation, constipation, hair loss, "eye pain", headaches not associated with changes in vision, loose stools, reduced appetite (each occurred in one subject) and mild nausea (4 subjects).

Discussion

Findings of putative antidepressant effects of open-label CoQ10 in a cohort of older adults with bipolar depression suggest that mitochondrial enhancing therapies may play a role in the treatment of affective illness. Study results also suggest specific symptom domains such as lassitude, apparent sadness and poor concentration may preferentially respond to such energy enhancing therapies. Although limited by an open label design, a small study sample and allowing for inclusion of concomitant medications, these findings provide initial proof-of-concept scientific evidence for antidepressant effects of the mitochondrial energy enhancing and antioxidant compound CoQ10 when used as adjunctive therapy for older adults with bipolar depression.

A neuroprogressive hypothesis of bipolar disorder has developed that implicates the neurobiological mechanisms of inflammation, glutamatergic excitotoxicity, oxidative stress and mitochondrial dysfunction in the pathophysiology of neuronal damage and cognitive impairment in bipolar disorder with advancing age.¹⁷ Previous treatment studies that included aging cohorts of individuals with bipolar depression were not designed to address these underlying neurobiological mechanisms. CoQ10 has both anti-oxidant and mitochondrial enhancing effects, providing a neurobiological rationale for adjunctive use of CoQ10 in clinical studies of bipolar depression. Confirmation of these findings using a

double-blinded randomized design is essential before the use of CoQ10 as a treatment for bipolar depression could be recommended.

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Table 1
Concomitant psychotropic medications, mean daily dose

Subject	Psychotropic Meds (Daily dose)
1	donepezil 10mg, lamotrigine 150mg
2	divalproex 750mg, quetiapine 100/100/200, Omega 3 FA 2000mg, lorazepam 1mg prn
3	lamotrigine 87.5 mg
4	Omega 3 FA (unk dose)
5	paroxetine 40 mg, venlafaxine 150 mg, trazadone 50g, buspirone 80mg
6	venlafaxine 60mg, lithium 1500mg, bupropion 300mg
7	lithium 600mg, escitalopram 20mg
8	venlafaxine 150mg, divalproex 250mg, bupropion 250mg, methylphenidate 25mg
9	lithium 1200 mg, lamotrigine 100mg
10	oxcarbazepine 1800mg, olanzapine 25mg, lorazepam 0.5mg/0.5mg PRN
11	paroxetine 25mg
12	none
13	zolpidem 10mg, clonazepam 1mg, Omega 3 FA 1000mg
14	quetiapine 200mg, lamotrigine 200mg, trazadone 50mg, Methylphenidate 20mg, clonazepam 1mg
15	lamotrigine 50mg
16	desvenlafaxine 100mg, oxcarbazepine 900mg, clonazepam 1mg
17	none
18	Omega 3 FA 240mg, gabapentin 2400mg, lamotrigine 200mg, venlafaxine 37.5mg, quetiapine 100mg
19	citalopram 40mg, lamotrigine 100mg