HHS Public Access

Author manuscript

J Clin Psychopharmacol. Author manuscript; available in PMC 2016 January 04.

Published in final edited form as:

J Clin Psychopharmacol. 2013 October ; 33(5): 627–635. doi:10.1097/JCP.0b013e31829a83f5.

A Placebo-Controlled Trial of Acetyl-L-Carnitine and α-Lipoic Acid in the Treatment of Bipolar Depression

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Abstract

Background—Bipolar disorder may be associated with mitochondrial dysfunction. Therefore, agents that enhance mitochondrial functioning may be efficacious in bipolar disorder. We performed a randomized placebo-controlled trial of the mitochondrial enhancers acetyl-L-carnitine (ALCAR) and α-lipoic acid (ALA) in patients with bipolar depression, and assessed markers of cerebral energy metabolism using phosphorus magnetic resonance spectroscopy.

Methods—We administered ALCAR (1000–3000 mg daily) plus ALA (600–1800 mg daily) or placebo for 12 weeks to 40 patients with bipolar depression and obtained imaging data at baseline, week 1, and week 12 of treatment in 20 patients using phosphorus 3-dimensional chemical-shift imaging at 4 T. Statistical analysis used random effects mixed models.

Results—We found no significant difference between ALCAR/ALA and placebo on change from baseline in the Montgomery-Asberg Depression Rating Scale in both the longitudinal (mean difference [95% confidence interval], −1.4 [−6.2 to 3.4], $P = 0.58$) and last-observation-carried-forward (−3.2 [−7.2 to 0.9], $P = 0.12$) analyses. ALCAR/ALA treatment significantly reduced phosphocreatine levels in the parieto-occipital cortex at week 12 ($P = 0.002$). Reduction in whole brain total nucleoside triphosphate levels from baseline to week 1 was associated with reduction in Montgomery-Asberg Depression Rating Scale scores ($P = 0.02$) in patients treated with ALCAR/ALA. However, this was likely a chance finding attributable to multiple statistical comparisons.

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AUTHOR DISCLOSURE INFORMATION

B.P.B. has received research grant support from Eli Lilly. J.I.H. has received research grant support from Eli Lilly, Ortho-McNeil Janssen Scientific Affairs, and Otsuka, and has been a consultant for Alkermes, Eli Lilly, Pfizer, Roche, and Shire. H.G.P. has received research grant support from Solvay Pharmaceuticals. P.F.R. has received research grant support from GlaxoSmithKline and Roche, has been a consultant to Novartis, Roche, Ridge Diagnostics, and Kyowa Hakko Kirin, owns stock in Ridge Diagnostics, and has received royalty payments from Repligen. None of the other authors reported any biomedical financial interests or potential conflicts of interest.

Conclusions—Treatment with ALCAR and ALA at the dose and duration used in this study does not have antidepressant effects in depressed bipolar patients and does not significantly enhance mitochondrial functioning in this patient group.

Keywords

bipolar disorder; depression; mitochondria; acetyl-L-carnitine; α-lipoic acid

Bipolar disorder is a common and often disabling mental illness. The depressive phase of bipolar disorder frequently dominates the illness and results in significant morbidity and mortality.[1] Several pharmacologic treatments including lithium, anticonvulsants, and antipsychotic medications have demonstrated efficacy in the depressed phase of bipolar disorder,[2,3] but many patients fail to respond or cannot tolerate first-line mood-stabilizer treatments.[4] Furthermore, traditional monoaminergic antidepressant agents may not outperform mood stabilizers alone in such patients.[5] Thus, novel treatment strategies for bipolar depression are needed.

Recent research suggests that abnormal mitochondrial functioning may contribute to bipolar disorder.[6] Although this dysfunction is insufficient to produce a systemic metabolic disorder, it could produce a brain disorder, because the brain requires much larger amounts of energy than other organs.[7] Evidence for this hypothesis comes from studies demonstrating a variety of findings in patients with bipolar disorder including (1) abnormalities in several neurochemical markers of cerebral energy metabolism on both proton (^{1}H) and phosphorus (^{31}P) magnetic resonance spectroscopy (MRS)[8]; (2) decreased expression of nuclear genes encoding for proteins involved in mitochondrial energy production on postmortem examination of hippocampal tissue[9]; (3) decreased lymphocytic expression of genes regulating oxidative phosphorylation, and impaired up-regulation of genes encoding for proteins of the electron transport chain after exposure to glucose deprivation[10]; (4) markedly abnormal mitochondrial morphology and distribution on postmortem examination of neurons and glia[11]; and (5) elevated lactate levels in cerebrospinal fluid (CSF).[12]

Consequently, certain bipolar patients might respond poorly to current treatments because mitochondrial dysfunction compromises cerebral energy metabolism. Therefore, treatments that enhance mitochondrial functioning may represent a novel therapeutic approach to bipolar disorder. Acetyl-L-carnitine (ALCAR), a naturally occurring mitochondrial metabolite, improves mitochondrial function and energy production in both animals and humans.[13–17] Moreover, several placebo-controlled trials have found ALCAR efficacious in various depressive spectrum disorders,[18–27] making it an intriguing candidate treatment for the depressed phase of bipolar disorder.

However, although ALCAR may increase energy production, it may also increase production of reactive oxygen species[28]—damaging mitochondrial DNA, proteins, and lipids, and thus further exacerbating defects in energy production. α-Lipoic acid (ALA), a mitochondrial coenzyme, is a potent antioxidant,[28] and thus an ideal companion agent with ALCAR to increase mitochondrial metabolic activity without increasing oxidative stress. Indeed, animal studies have demonstrated that the ALCAR/ALA combination improves

mitochondrial functioning by increasing metabolism and lowering oxidative stress more than either compound alone[28–30] and combined mitochondrial-enhancing compounds have shown more promise than single agents for the treatment of mitochondrial disorders.[31] Both ALCAR and ALA easily cross the blood-brain barrier,[32,33] possess favorable adverse-effect profiles, and are widely available as over-the-counter supplements, making them especially attractive as potential bipolar disorder treatments.

We hypothesized that ALCAR/ALA would demonstrate significantly greater efficacy than placebo as an augmentation treatment in bipolar depressed patients displaying an incomplete response to conventional treatments. Accordingly, we performed a 12-week placebo-controlled, double-blind, parallel-group, flexible-dose study of ALCAR 1000 to 3000 mg daily plus ALA 600 to 1800 mg daily, added to conventional treatment in depressed bipolar patients.

Additionally, using ^{31}P-MRS, we assessed in vivo changes in mitochondrial functioning by measuring several biological markers of cerebral energy metabolism during treatment. Specifically, we hypothesized that ALCAR/ALA, but not placebo, at both week 1 and week 12, would produce increased cerebral concentrations of phosphocreatine (PCr), a compound that serves as a reservoir for high-energy phosphates, and β-nucleoside triphosphate (β-NTP), which is widely acknowledged as the best index of brain levels of adenosine triphosphate (ATP). We also hypothesized that ALCAR/ALA treatment would increase cerebral intracellular pH (pH) due to decreased lactate production resulting from a reduced dependence on glycolysis for energy production. Our primary brain region of interest was the anterior cingulate cortex (ACC)—a region implicated in the pathophysiology of bipolar disorder.[34,35] We also performed exploratory analyses of the previously mentioned metabolites and pH across the whole brain and in several other brain regions including the parieto-occipital cortex (POC), frontal cortex, and thalamus.

MATERIALS AND METHODS

Study Design

We assigned eligible participants to ALCAR/ALA or placebo, in a 1:1 ratio, via a computer-generated randomization schedule. An independent research assistant, not otherwise involved with the study, placed ALCAR and ALA or matching placebo capsules (all obtained from Pure Encapsulations, Sudbury, MA) in numbered bottles, which were assigned sequentially to study participants at randomization. All participants and study personnel remained blinded to treatment assignments until study termination.

ALCAR/ALA dosing was based on previous clinical trials reporting tolerability and efficacy.[23,36,37] Given the lack of experience with these compounds in the treatment of bipolar disorder, we used a flexible-dose design to achieve the highest tolerated doses and hence a maximum chance of biological effect.

A total sample size of 40 was chosen because it had greater than 80% power to detect a 4-point difference between groups in Montgomery-Asberg Depression Rating Scale (MADRS)

scores over 12 weeks, assuming a standard deviation for repeated measures of MADRS of 6, and a within-subject correlation of 0.6.

Participant Selection

We recruited participants aged 18 to 55 years, meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for bipolar disorder (type I or II), currently depressed, scoring greater than or equal to 20 on the MADRS at screening and baseline. Exclusion criteria were (1) inability to provide written informed consent; (2) history of schizophrenia or obsessive-compulsive disorder; (3) active psychosis; (4) active suicidality; (5) alcohol or substance dependence (other than nicotine) within 3 months of enrollment; (6) electroconvulsive therapy within 3 months of enrollment; (7) positive urine drug screen for substances of abuse; (8) history of mitochondrial disorder; (9) current pregnancy or lactating; and (10) history of seizure disorder, organic brain disease, or clinically significant medical disease. To limit heterogeneity in the imaging sample, we accepted only type I bipolar disorder participants for the imaging component of the study.

Participants continued their current psychiatric medications, provided they had been on stable doses for at least 4 weeks before enrollment and required no significant dose changes during the study. Rarely, minor dose adjustments were permitted if recommended by the participant's outpatient psychiatrist and judged unlikely to influence depressive symptoms (see later). Participants were permitted to continue as-needed medications as long as the dose and frequency of use did not change significantly during the course of the study.

Clinical Evaluation

Participants initially received a screening evaluation, where they signed informed consent for the study, which had been approved by the McLean Hospital Institutional Review Board. We then obtained basic demographic information, medical and psychiatric history, the Structured Clinical Interview for *DSM-IV* (SCID) to establish the diagnosis of bipolar depression and any other comorbid Axis I disorders, physical examination, vital signs, electrocardiogram, and laboratory tests. We then administered our primary clinical outcome measure, the MADRS, and 3 secondary measures, namely, the 25-item Hamilton Depression Rating Scale (HAM-D), Clinical Global Impression Scale for Severity (CGI-S), and Young Mania Rating Scale (YMRS).

Eligible participants returned in approximately 1 week for a baseline visit to assess adverse events, concomitant medications, vital signs, MADRS, HAM-D, CGI-S, and YMRS. Additionally, those eligible for the MRS component of the study underwent a ^{31}P-MRS scan (detailed later). All participants were then started on either 2 ALCAR (500 mg) capsules and 1 ALA (600 mg) capsule daily or matching placebo, with instructions to take study medication at least 30 minutes before or 60 minutes after eating, because food impairs absorption of ALA.[38]

Absent dose-limiting adverse effects, ALCAR, and ALA were increased to 1000 mg twice daily and 600 mg twice daily, respectively, at week 1 and to 1000 and 600 mg 3 times daily, respectively, at week 2. Participants unable to tolerate higher doses could reduce to a

minimum dose of 1000 and 600 mg daily. Participants were seen at weeks 1, 2, 3, 4, 6, 8, 10, and 12. At each visit, we administered the same outcome measures as at baseline, plus the Clinical Global Impression Scale for Improvement. We also assessed for adverse events and changes in concomitant medications and performed pill counts to assess compliance. Additional ^{31}P-MRS scans were performed at week 1 and at week 12 for those participating in the MRS component of the study.

^{31}P-MRS Acquisition

A dual tuned proton-phosphorus TEM head coil (Bioengineering Inc, Minneapolis, MN) operating at 170.3 MHz for proton and 68.95 MHz for phosphorus was used for all anatomical imaging and spectroscopy. Manual shimming on the unsuppressed global water signal yielded a typical unsuppressed water linewidth of 20 to 30 Hz. A 3-plane scout image set quickly determined the patient's position within the coil, followed by high-contrast, T1-weighted sagittal and axial image sets (TE/TR = 6.2/11.4 milliseconds, field of view = 22 × 22 cm, readout duration = 4 milliseconds, receive bandwidth = ±32 kHz, in-plane matrix size = 128 × 256 [sagittal], 256 × 256 [axial], in-plane resolution = 1.90 × 0.94 mm [sagittal], 0.94 × 0.94 mm [axial], axial-plane matrix size = 32 [sagittal], 64 [axial] axial-plane resolution = 2.5 mm [sagittal and axial], scan time = 2 minutes, 30 seconds [sagittal], 5 minutes [axial]) of the entire brain were acquired using a 3-dimensional, magnetization-prepared FLASH imaging sequence (3D-mpFLASH), allowing for clear segmentation between gray matter, white matter, and CSF.

Phosphorus 3-dimensional chemical-shift imaging (^{31}P 3D-CSI) used the phosphorus channel of the dual tuned proton-phosphorus head coil. Acquisition parameters were as follows: TR = 500 milliseconds; tip angle = 32 degrees; Rx bandwidth = ±2 kHz; complex points = 1024; readout duration = 256 milliseconds; prepulses = 10; preacquisition delay = 1.905 milliseconds; field of view (x,y,z) = 330 mm; nominal volume = 13.1 mL; maximum phase-encode matrix dimension (x,y,z) 14 × 14 × 14 (zero-filled out to 16 × 16 × 16 before reconstruction). The ^{31}P 3D-CSI sequence used a spherically bound, sparse-omission,[18–20] reduced phase-encoding scheme, with k-space points randomly omitted from the 14 × 14 × 14 matrix in such a way that the degree of k-space point omission gradually increased toward outer k-space. The variable k-space sampling density preserved the sensitivity of the measurement as well as the spatial localization, although greatly reducing scan time.

^{31}P-MRS Processing and Analysis

The ^{31}P 3D-CSI raw data sets were first zero-padded within a 16 × 16 × 16 matrix and each k-space free-induction decay digitally corrected in amplitude, accounting for the discrepancy between theoretical and integer-weighted k-space filter functions. Once spatially resolved, the ^{31}P 3D-CSI grid was coregistered with the axial T1-weighted images such that the grid was centered midsagittally inside the brain according to anatomical landmarks in both the sagittal and axial planes (Fig. 1). A 4 × 7 × 3 matrix of voxels was centered within the brain so as to exclude voxels adjacent to the temporalis muscle, thus minimizing signal contamination from these muscles. Additionally, voxels too close to the superior and inferior surfaces of the skull were omitted due to low signal-to-noise and susceptibility artifact. Automated software then zero-order phase-corrected each spectrum using the PCr resonance

as a navigator and extracted the spatially resolved spectral free-induction decays (time-domain) from each voxel in each scan for separate fitting of each spectrum.

Offline image processing used commercial and custom-written software for tissue segmentation, partial-volume analysis, and grid-shifting. For ^{31}P 3D-CSI spectral fitting, we used a spectral time-domain fitting program, based on the Marquardt-Levenberg nonlinear, least-squares algorithm, incorporating prior knowledge of spectral peak assignments, chemical-shifts, and J-coupling constants.[39] Our spectral model included 10 phosphorus-containing molecules: γ-, α-, and β-NTP, phospho-ethanolamine (Petn), phosphocholine (Pcho), glycerophospho-ethanolamine (GPEtn), glycerophosphocholine (GPCho), 2,3 diphosphoglyceride (DPG), inorganic phosphate (Pi), membrane-bound phospholipid (MP), and PCr (Fig. 2). The model assumes Lorentzian lineshape for the singlet PCr and Pi resonances, Lorentzian doublets (1:1) for the γ- and α-NTP resonances and a Lorentzian-modeled triplet structure (1:2:1) for the β-NTP resonance where the NTP J-coupling constant was fixed to 16 Hz. Membrane phospholipid was modeled as a single broad resonance in the phosphodiester region and fixed in chemical shift and linewidth. The dinucleotide (DN) peak was modeled as a Lorentzian singlet fixed in chemical shift and linewidth. The individual constituents for the phosphomonoester (Petn and Pcho) and phosphodiester (GPEtn and GPCho) regions were all modeled as Gaussian singlets because our 4T spectra are coupled and J-coupled dispersion still exists within each one of these phospholipid resonances, thus affecting the lineshape. The linewidth of each resonance as well as the chemical shift of the lower signal-to-noise peaks such as the DPG, Pcho, GPEtn, MP, and DN resonances were constrained. Our spectral model is described in more detail elsewhere.[39]

Estimates of pH were calculated using the chemical shift difference between the resonances for PCr and Pi according to the modified Henderson-Hasselbalch equation.[40] A measure of total NTP (α-, β-, and γ-NTP) was also calculated.

Tissue Segmentation and Image Postprocessing

Extracted brain images were then segmented into white matter, gray matter, and CSF using the FSL Brain Extraction Tool (FMRIB)'s Automated Segmentation Tool (FAST). We then determined the contributions of tissue type (gray or white matter) and CSF in each voxel. In this process, we convolved the mathematically modeled, 3-dimensional point-spread function (3D-PSF) from the sparse k-space sampling scheme, digitally sampled in a 256 × 256 × 64 matrix, with the coregistered binary images (also digital matrices of 256 × 256 × 64) to obtain theoretically correct pixel counts of the contribution of each tissue type to each voxel based on the 3D-PSF weighted distribution.[39]

Statistical Analysis

Baseline group characteristics were compared by Fisher exact tests for categorical variables and 2-sample *t* tests for continuous variables.

The primary efficacy analysis was a longitudinal random regression analysis comparing the rate of change of the outcome variables (MADRS, HAM-D, CGI-S, and YMRS) during the

treatment period between groups. We used a model for the mean of the outcome variable that included terms for treatment, time (as a continuous variable), and treatment-by-time interaction. The coefficient for the treatment-by-time term quantifies the rate of clinical improvement, which we expressed as the estimated change in the measure at week 12. We also conducted a secondary analysis comparing change from baseline to end point (using last observation carried forward) between groups using the 2-sample *t* test.

We compared the groups on ^{31}P-MRS measures using a similar longitudinal random regression model with terms for the ^{31}P-MRS measure, time (modeled as a categorical variable), and treatment-by-time interaction. The coefficients for the 2 treatment-by-time interaction terms represent the estimated difference in the ^{31}P-MRS measure between groups at week 1 and at week 12, adjusted for baseline values. We first assessed whether there was a significant treatment-by-time interaction (2 degrees of freedom χ^2 test), and if there was, we then examined the coefficients for the individual interaction terms to determine whether they were statistically significant.

For all longitudinal analyses, we used generalized estimating equations to adjust standard errors to account for the correlation of observations within individuals, with the working covariance structure being first-order autoregressive for the models where time was a continuous variable and independence for the models where time was a categorical variable.

We used linear regression to assess associations between improvement in depressive symptoms (change in MADRS from baseline using LOCF) and baseline levels of ^{31}P-MRS metab-olites and pH, as well as change in these metabolites at week 1 and week 12 in each brain region (ACC, POC, frontal cortex, thalamus, and whole brain).

All analyses were performed using Stata 9.2 software. α was set at 0.05, 2-tailed.

RESULTS

Clinical Trial Analyses

Participant Characteristics and Study Flow—Sixty-eight participants signed informed consent for the study from September 4, 2008, to January 25, 2011. Of these, 28 were withdrawn from the study before receiving treatment (lost to follow-up [n = 14]; did not meet inclusion criteria [n = 7]; met exclusion criteria [n = 5]; consent withdrawn [n = 2]). Forty were randomized to treatment and all received at least 1 postbaseline assessment. Of the 20 participants randomized to each study arm, 11 (55%) in the ALCAR/ALA group and 14 (70%) in the placebo group completed study procedures. Reasons for discontinuation included adverse event (n = 5), noncompliance with study procedures (n = 3), and consent withdrawn (n = 1) in the ALCAR/ALA group and adverse event (n = 4) and consent withdrawn (n = 2) in the placebo group.

Participants were non-Hispanic white (n = 38) and African American (n = 2). The ALCAR/ALA and placebo groups showed similar age, sex, bipolar type, baseline depression severity, and concomitant psychiatric medications (Table 1). Mean (SD) daily doses of ALCAR and ALA at end point were 2275 (750.6) and 1365 (450.4) mg, respectively. Three

participants were permitted to alter existing medications during the study. One, receiving ALCAR/ALA, was permitted to increase citalopram from 20 to 40 mg daily at week 1. This participant withdrew at week 6 due to worsening depressive symptoms. Another, receiving placebo, was permitted to increase quetiapine from 100 to 150 mg at bedtime at week 2. This participant withdrew at week 4. Another, receiving ALCAR/ALA, was permitted to switch at week 6 from eszopiclone 3 mg to zolpidem 10 mg at bedtime due to a change in prescription drug coverage.

Efficacy Analyses—Mean MADRS scores for each treatment group are presented in Figure 3. Neither the primary longitudinal analysis nor the end point analysis showed significant differences between ALCAR/ALA and placebo on any outcome measure (Table 2).

Adverse Events—Adverse events were generally minor. The most frequently reported adverse events in the ALCAR/ALA group versus the placebo group included diarrhea (30% ALCAR/ALA vs 15% placebo), foul-smelling urine (25% vs 5%), rash (20% vs 0%), constipation (15% vs 5%), and dyspepsia (15% vs 0%). There were 2 serious events. One participant was withdrawn from the study when hospitalized for acute chest pain; cardiac evaluation proved unremarkable and the participant was found to be taking placebo. Another participant, receiving ALCAR/ALA, developed abdominal pain, found due to small bowel obstruction, 31 days after completing study medication. Given this time interval, the event was judged unrelated to study treatment. Additionally, 1 participant receiving ALCAR/ALA displayed mildly elevated liver function tests at study completion, felt likely due to concomitant treatment with valproate.

^{31}P-MRS Analyses

Twenty participants (10 receiving ALCAR/ALA, 10 receiving placebo) participated in the imaging component of the study. Because of attrition, only 12 of these (5 ALCAR/ALA and 7 placebo) yielded complete imaging data sets. We found virtually no group differences for changes from baseline in metabolite or pH levels (ie, significant treatment-by-time interactions in our model), including a posteriori analysis of changes in total NTP, at week 1 or week 12 (Table 3). We found no significant association between change in any of our primary ^{31}P-MRS measures and change in MADRS in any of the regions examined. In a posteriori analyses involving total NTP, we found a significant association between change in whole brain total NTP and change in MADRS at week 1 ($P = 0.02$).

DISCUSSION

In a randomized, placebo-controlled, double-blind, parallel-group trial including 40 patients with bipolar depression, we found no significant difference in the antidepressant effects of a mitochondrial enhancement treatment consisting of ALCAR plus ALA versus placebo. Furthermore, in a subgroup of 20 participants evaluated with ^{31}P-MRS, we found no significant change in brain levels of the high-energy phosphate compounds PCr and β-NTP or in pH at weeks 1 and 12 of ALCAR/ALA treatment. Overall, our data suggest that

ALCAR/ALA, at the dose and duration used here, neither significantly reduces depressive symptoms nor enhances mitochondrial functioning in depressed bipolar patients.

Although our findings argue against further exploration of ALCAR/ALA (at least at the doses used here) for treatment of bipolar depression, other mitochondrial-enhancing compounds, such as N-acetylcysteine (NAC), coenzyme Q10 (CoQ10), and creatine monohydrate, might have more potent effects on mitochondrial functioning and hence greater antidepressant efficacy. For instance, Berk et al[41] found that NAC (which increases synthesis of the potent antioxidant glutathione), added to treatment-as-usual in bipolar patients, significantly decreased depressive symptoms and improved quality of life compared to placebo. However, these investigators administered NAC for 24 weeks—twice the duration of our study—and found a significant NAC-placebo difference only after week 20, suggesting that mitochondrial supplements might require more time to yield clinical benefit. Moreover, although we enrolled only depressed bipolar patients, Berk et al examined NAC as a maintenance treatment, enrolling bipolar patients irrespective of current mood state. Therefore, mitochondrial enhancers such as NAC might be best, not as treatments of acute mood episodes, but as add-on maintenance therapies to manage difficult-to-treat subsyndromal symptoms—an area of great clinical need.[42] However, a recent open-label study[43] by the same group found a significant reduction in depressive symptoms after only 8 weeks of NAC treatment in patients with bipolar depression. Importantly, in addition to its effects on glutathione synthesis, NAC affects glutamatergic neurotransmission,[44] which has also been implicated in the pathophysiology of bipolar disorder.[34] Therefore, further investigation into the exact mechanism(s) of action of NAC is warranted. Recently, an open-label study of CoQ10 in geriatric patients with bipolar depression demonstrated antidepressant effects early in treatment, which dissipated by the end of the 8-week study,[45] supporting further investigation in larger controlled trials.

We were surprised to find little effect of ALCAR/ALA on ^{31}P-MRS markers of cerebral energy metabolism. ALCAR is thought to exert many of its biological effects through the action of its carnitine and acyl moieties. Specifically, carnitine is important in the transport of fatty acids into mitochondria to undergo β-oxidation—an important source of mitochondrial energy production[46,47]—and acylcarnitines, when oxidized within mitochondria, release energy and form acetyl-CoA, which enters the tricarboxylic acid cycle.[48] Through these mechanisms, ALCAR is hypothesized to boost mitochondrial efficiency, increasing ATP production. Accordingly, adult and aged rats administered ALCAR show both an increase in ATP and PCr as measured by ^{31}P nuclear magnetic spectroscopy.[49] However, our imaging analyses yield only 2 significant associations (see above) —and these likely represented chance findings, given the number of comparisons made and the fact that both were counter to the hypothesized direction of change for these metabolites.

Several hypotheses might explain our negative findings. First, the small imaging sample size (only 12 participants yielded complete ^{31}P-MRS data sets) increases the likelihood for type II error. Second, the dose of ALCAR/ALA may have been inadequate to achieve the desired biological effect—particularly at week 1 when participants were only taking 1000 mg/600 mg daily. Third, as mentioned previously, 12 weeks of ALCAR/ ALA treatment may have

been too brief to benefit mitochondrial functioning. Fourth, lacking ^{31}P-MRS data from a control group, we could not calibrate the extent of mitochondrial dysfunction in our study population, and hence cannot exclude a ceiling effect. In other words, our participants who contributed imaging data may have had normal PCr and β-NTP levels to begin with, and thus showed minimal increase in PCr and β-NTP levels with ALCAR/ALA treatment. Fifth, in contrast to animal data, the effects of ALCAR/ALA on human mitochondrial functioning may be too weak to significantly impact the neuroimaging markers of cerebral energy metabolism used in our study. Indeed, little is known about the effects of ALCAR/ALA on cerebral energy metabolism in humans; to our knowledge, the only other in vivo study besides ours examined 2 patients with geriatric depression.[23] This study found improvement in depression after 12 weeks of ALCAR 3 g/d, and improvement was associated with increased levels of PCr in the prefrontal cortex as measured by ^{31}P-MRS. However, geriatric depression may respond differently to ALCAR, given the effects of aging on mitochondrial functioning and cerebral bioenergetics.[50]

It is important to note several limitations of this study. First, the sample size was small, limiting statistical power. Second, we did not place restrictions on concomitant medications during the course of the study. Although this approach increases the potential generalizability of our results, it runs the risk of obscuring between-group differences. Third, we enrolled patients with both type I and type II bipolar disorder, increasing the biological heterogeneity of our sample. Although we found no evidence for differences in efficacy based on bipolar type in our study, it is theoretically plausible that mitochondrial dysfunction may be more prevalent in a particular subtype of bipolar disorder. Therefore, a more homogenous sample of bipolar patients could be more biologically predisposed to benefit from ALCAR/ALA treatment. Fourth, as discussed previously, we did not include a non–bipolar disorder comparison group in the imaging study, making it difficult to assess the degree of mitochondrial dysfunction at baseline in our study cohort. Fifth, evidence suggests that intravenous administration of ALCAR may be necessary to achieve antidepressant effects[27] given its nonlinear pharmacokinetics[51] and low absolute bio-availability.[52,53] Therefore, it is possible that oral ALCAR/ ALA, as administered in this study, did not result in sufficient brain concentrations to significantly impact cerebral mitochondrial functioning.

In summary, although our findings may discourage further investigation of ALCAR/ALA for treatment of bipolar depression, they should not discourage the study of other potentially beneficial mitochondrial-enhancing agents for bipolar disorder—especially maintenance treatment to address subthreshold mood symptoms. Although substantial evidence suggests a role for mitochondrial dysfunction in the pathophysiology of bipolar disorder, the cause of this dysfunction remains obscure, making it difficult to develop targeted treatments. Furthermore, few drug treatments have been developed to enhance mitochondrial functioning through specific biological pathways. As a result, most available mitochondrial-modulating compounds are low-potency over-the-counter supplements with inexact mechanisms of action. Nevertheless, emerging findings suggest that at least one of these mitochondrial enhancers, NAC, may have potential use in depressed bipolar patients.

In short, despite the negative results of the present study, it seems important to pursue the specific molecular underpinnings of mitochondrial dysfunction in bipolar disorder, and to develop more targeted and potent mitochondrial enhancers. Progress in this area may create new opportunities for treatment of this serious and often refractory condition.

Acknowledgments

This study was supported by grants from the Stanley Medical Research Institute, the Sidney R. Baer, Jr. Foundation through a NARSAD Young Investigator Award (B.P.B.), and the National Institutes on Drug Abuse (NIDA) Grant T32-DA07252 (B.P.B.). In addition, B.P.B. was supported by the Clinical Investigator Training Program (CITP) through the Beth Israel Deaconess Medical Center-Harvard/MIT Health Sciences and Technology, in collaboration with Pfizer Inc and Merck & Co.

The authors thank Pure Encapsulations for providing ALCAR, ALA, and matching placebo capsules for this study (note: Pure Encapsulations provided no additional financial support for this study and had no input into the design or analysis of this study).

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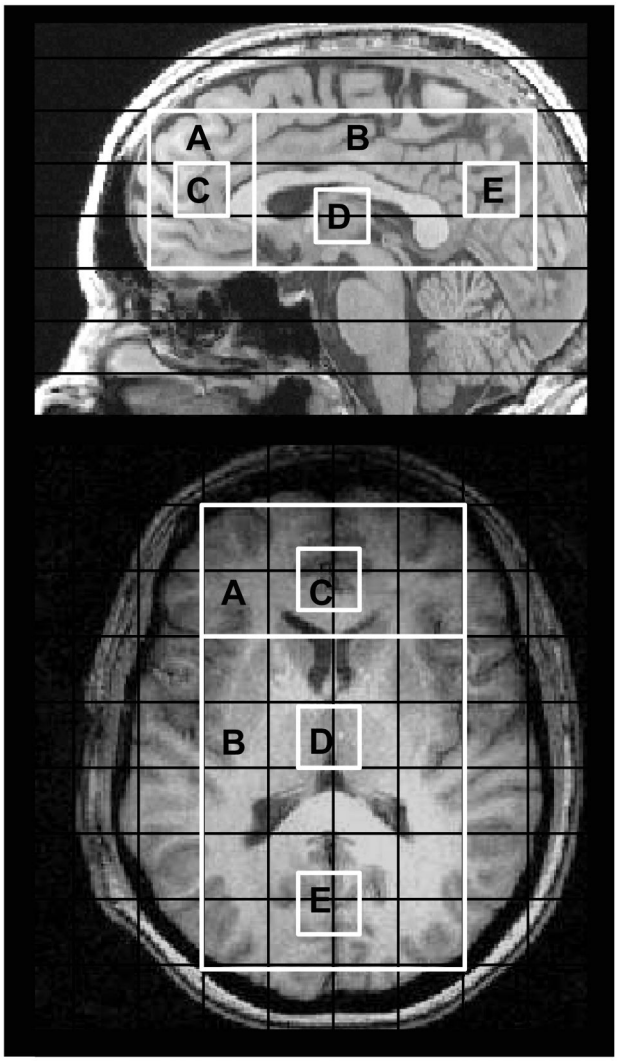

FIGURE 1.

T1-weighted sagittal and axial images depicting the CSI-grid overlay and the various subregions studied. Regions include (A) frontal cortex, (B) whole brain, (C) ACC, (D) thalamus, and (E) POC.

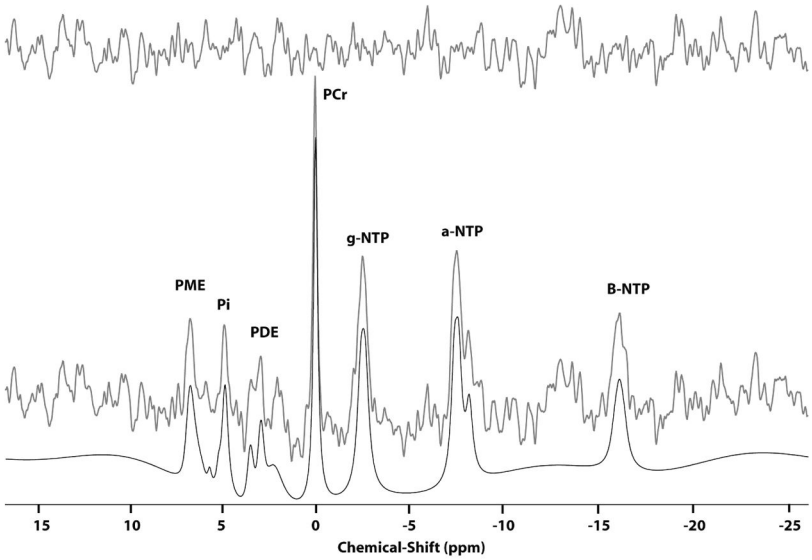

FIGURE 2.

Sample ^{31}P-MRS spectrum from a single voxel showing fit, residual, and labeled metabolites. PCr indicates phosphocreatine; PDE, phosphodiesters; Pi, inorganic phosphate; PME, phosphomonoesters; a-NTP, α-nucleoside triphosphate; B-NTP, β-nucleoside triphosphate; g-NTP, γ-nucleoside triphosphate.

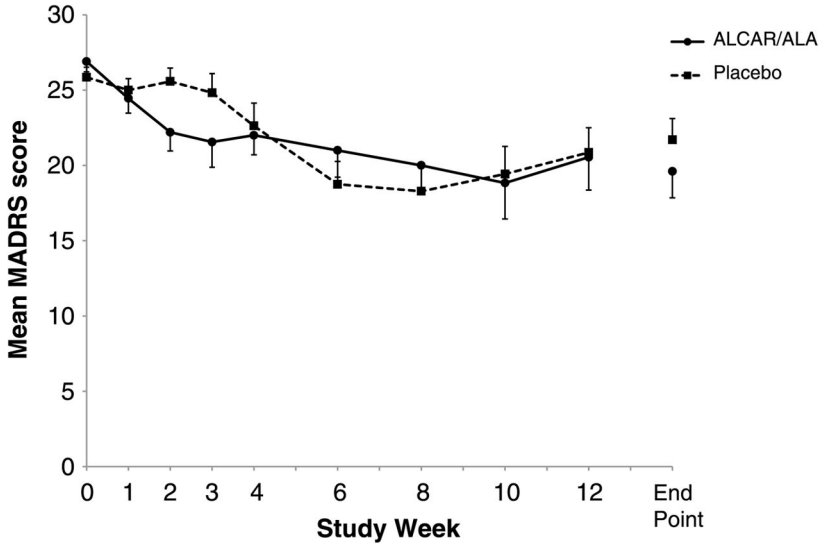

FIGURE 3.

The mean scores on the MADRS over 12 weeks of treatment with ALCAR plus ALA or placebo. Error bars represent standard error.

TABLE 1

Demographic and Clinical Characteristics of the Subjects

Characteristic	Randomized to ALCAR/ALA (n = 20)	Randomized to Placebo (n = 20)	Analysis	
			t	*P*
Age, mean (SD), y	46 (10.3)	44.9 (11.9)	−0.33	0.75*
Sex, n (%)				0.75†
Male	9 (45)	7 (35)		
Female	11 (55)	13 (65)		
Bipolar type, n (%)				0.27†
Type I	17 (85)	13 (65)		
Type II	3 (15)	7 (35)		
MADRS score, mean (SD)	26.9 (3.1)	25.9 (3.0)	−1.1	0.28*
HDRS score‡, mean (SD)	23.3 (3.5)	22.1 (3.2)	−1.1	0.27*
YMRS score‡, mean (SD)	2 (2.1)	2.4 (2.1)	0.61	0.54*
CGI-S score‡, mean (SD)	4.6 (0.5)	4.6 (0.51)	0.31	0.76*
Concomitant medications, n (%)§				
Valproate	6 (30)	2 (10)		
Lithium	5 (25)	4 (20)		
Lamotrigine	7 (35)	9 (45)		
Antipsychotics	18 (90)	12 (60)		
Antidepressants	14 (70)	14 (70)		
Benzodiazepines	10 (50)	14 (70)		
Others	8 (40)	14 (70)		

*By *t* test (2-tailed).

†By Fisher exact test (2-tailed).

‡Score at baseline (day of randomization).

§There were no significant group differences in concomitant medications by Fisher exact test (2-tailed).

TABLE 2

Values of Outcome Measures After 12 Weeks of Treatment (Completers and LOCF) and Model-Based Estimates of Differences Between the Groups

	Completers		LOCF					
	ALCAR/ALA (n = 11)	Placebo (n = 14)	ALCAR/ALA (n = 20)	Placebo (n = 20)	Longitudinal Analysis, Mean 12-wk Change		End Point Analysis, Mean 12-wk Change	
Outcome Measure	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
MADRS score	20.5 (7.2)	20.9 (6.2)	19.6 (7.9)	21.7 (6.3)	−1.4 (−6.2 to 3.4)	0.58	−3.2 (−7.2 to 0.9)	0.12
HAM-D score	17.8 (5.6)	17.9 (5.9)	17.5 (6.4)	18.5 (6.2)	−0.9 (−5.3 to 3.4)	0.92	−2.2 (−5.9 to 1.5)	0.23
YMRS score	1.4 (2.2)	2.1 (1.9)	1.7 (2.2)	2.1 (1.8)	−0.4 (−1.9 to 1.0)	0.58	0.05 (−1.3 to 1.4)	0.94
CGI-S score	4 (0.8)	4.1 (0.7)	4 (0.9)	4.2 (0.7)	−0.03 (−0.56 to 0.50)	0.92	−0.25 (−0.77 to 0.27)	0.34

CI indicates confidence interval.

J Clin Psychopharmacol. Author manuscript; available in PMC 2016 January 04.

TABLE 3

Mean (SD) Metabolite and pH Levels by Region[*†]

	PCr		β-NTP		pH		Total NTP	
	ALCAR/ALA	**Placebo**	**ALCAR/ALA**	**Placebo**	**ALCAR/ALA**	**Placebo**	**ALCAR/ALA**	**Placebo**
Baseline								
ACC	0.167 (0.032)	0.174 (0.028)	0.085 (0.012)	0.067 (0.025)	7.03 (0.067)	7.01 (0.075)	0.257 (0.037)	0.262 (0.044)
POC	0.162 (0.018)	0.157 (0.014)	0.065 (0.005)	0.062 (0.007)	7.02 (0.02)	7.03 (0.02)	0.234 (0.013)	0.226 (0.019)
Frontal cortex	0.191 (0.04)	0.174 (0.025)	0.067 (0.013)	0.068 (0.01)	6.98 (0.034)	6.99 (0.034)	0.24 (0.025)	0.245 (0.027)
Thalamus	0.173 (0.023)	0.169 (0.025)	0.067 (0.011)	0.066 (0.014)	7.02 (0.023)	7.02 (0.027)	0.241 (0.019)	0.244 (0.034)
Whole brain	0.173 (0.018)	0.166 (0.01)	0.065 (0.003)	0.065 (0.004)	6.99 (0.014)	6.99 (0.007)	0.230 (0.009)	0.233 (0.009)
Week 1								
ACC	0.177 (0.037)	0.156 (0.008)	0.07 (0.01)	0.08 (0.023)	6.99 (0.046)	7.03 (0.057)	0.244 (0.025)	0.252 (0.03)
POC	0.167 (0.011)	0.168 (0.02)	0.065 (0.006)	0.067 (0.011)	7.02 (0.036)	7.03 (0.017)	0.237 (0.009)	0.234 (0.025)
Frontal cortex	0.174 (0.022)	0.183 (0.038)	0.072 (0.015)	0.067 (0.016)	7.0 (0.022)	6.99 (0.031)	0.225 (0.025)	0.212 (0.017)
Thalamus	0.167 (0.022)	0.16 (0.016)	0.066 (0.005)	0.06 (0.02)	7.02 (0.024)	7.01 (0.021)	0.235 (0.014)	0.225 (0.021)
Whole brain	0.169 (0.014)	0.169 (0.012)	0.064 (0.004)	0.064 (0.005)	6.99 (0.007)	6.99 (0.008)	0.229 (0.011)	0.225 (0.008)
Week 12								
ACC	0.169 (0.002)	0.201 (0.041)	0.073 (0.01)	0.072 (0.006)	6.95 (0.063)	7.0 (0.128)	0.245 (0.069)	0.264 (0.036)
POC	0.149 (0.005)	0.17 (0.015)	0.066 (0.008)	0.066 (0.011)	7.01 (0.013)	7.03 (0.032)	0.234 (0.024)	0.233 (0.027)
Frontal cortex	0.186 (0.028)	0.186 (0.032)	0.065 (0.005)	0.066 (0.01)	6.99 (0.023)	6.97 (0.021)	0.229 (0.02)	0.23 (0.013)
Thalamus	0.162 (0.02)	0.165 (0.015)	0.064 (0.014)	0.068 (0.003)	6.92 (0.218)	7.0 (0.035)	0.237 (0.005)	0.242 (0.013)
Whole brain	0.163 (0.014)	0.17 (0.013)	0.064 (0.002)	0.065 (0.004)	6.99 (0.01)	6.99 (0.007)	0.229 (0.006)	0.232 (0.005)

[*] There were no significant group differences for change in metabolite or pH levels from baseline (ie, significant treatment-by-time interactions in our model assessed by 2 degrees of freedom χ^2 test [see text]), except for (1) PCr in the ACC ($P = 0.02$), but analysis of the individual interaction terms showed that levels at neither time point were significantly different from baseline; and (2) PCr in the POC ($P = 0.002$), with univariate analysis showing that week 12 was significantly decreased from baseline ($P = 0.003$).

[†] Metabolite levels are measured in arbitrary units.