

# A Placebo-Controlled Trial of Acetyl-L-Carnitine and $\alpha$ -Lipoic Acid in the Treatment of Bipolar Depression

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**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  $\alpha$ -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.

**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.

**Key Words:** bipolar disorder, depression; mitochondria, acetyl-L-carnitine,  $\alpha$ -lipoic acid

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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.<sup>1</sup> Several pharmacologic treatments including lithium, anticonvulsants, and antipsychotic medications have demonstrated efficacy in the depressed phase of bipolar disorder,<sup>2,3</sup> but many patients fail to respond or cannot tolerate first-line mood-stabilizer treatments.<sup>4</sup> Furthermore, traditional monoaminergic antidepressant agents may not outperform mood stabilizers alone in such patients.<sup>5</sup> Thus, novel treatment strategies for bipolar depression are needed.

Recent research suggests that abnormal mitochondrial functioning may contribute to bipolar disorder.<sup>6</sup> 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.<sup>7</sup> 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 (<sup>1</sup>H) and phosphorus (<sup>31</sup>P) magnetic resonance spectroscopy (MRS)<sup>8</sup>; (2) decreased expression of nuclear genes encoding for proteins involved in mitochondrial energy production on postmortem examination of hippocampal tissue<sup>9</sup>; (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<sup>10</sup>; (4) markedly abnormal mitochondrial morphology and distribution on postmortem examination of neurons and glia<sup>11</sup>; and (5) elevated lactate levels in cerebrospinal fluid (CSF).<sup>12</sup>

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.<sup>13–17</sup> Moreover, several placebo-controlled trials have found ALCAR efficacious in various depressive spectrum disorders,<sup>18–27</sup> 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<sup>28</sup>—damaging mitochondrial DNA, proteins, and lipids, and thus further exacerbating defects in energy production.  $\alpha$ -Lipoic acid (ALA), a mitochondrial coenzyme, is a potent antioxidant,<sup>28</sup> 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<sup>28–30</sup> and combined mitochondrial-enhancing compounds have shown more promise than single agents for the