# Myriad of implications of acetyl-L-carnitine deficits in depression

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The report of Nasca et al. (1) of low levels of acetyl-L-carnitine (LAC) in depression promises to have a major impact in the understanding and treatment of major depression. It may also have implications for other types of depressive illnesses such as bipolar disorder and even posttraumatic stress disorder (PTSD).

The findings are especially noteworthy from a number of different perspectives. They are from two different study populations, and the values are documented by two different assays. LAC levels were not only lower in depressed patients in general but lower in those with greater illness severity as well as an earlier age of onset, the latter of which is a risk factor for a poor outcome in adulthood. In those with a history of treatment-resistant depression (TRD), LAC was lower in females and those experiencing emotional neglect.

The convergence of these clinical findings with those in animal models of depression makes the potential implications even more striking. Low levels of LAC are found in several different models, and impressively, treatment of these animals with LAC resulted in rapid onset of improvement in their depressive-like behaviors. In an earlier paper in PNAS, Nasca et al. (2) reported that these effects of LAC were conveyed by an epigenetic mechanism involving rapid up-regulation of type 2 metabotropic glutamate (mGlu2) receptors, which are inhibitory to glutamate release. This occurred by increasing levels of acetylated H3K27 bound to the *Grm2* promoter, yielding increased transcription of *Grm2* in hippocampus and prefrontal cortex. The rapid increase in mGlu2 receptors was associated with improvement in depressive-like behaviors in 3 d as opposed to the usual 14 d of treatment required with the traditional tricyclic antidepressant (AD) clomipramine. The LAC also was associated with increases in BDNF and acetylation of NF-κB p65 subunit and improved insulin resistance.

Nasca et al. (1) were appropriately conservative in interpreting their findings and pointing out multiple directions for future studies. However, a commentator is not bound by such restrictions, and I will note a variety of potential implications that open new avenues for therapeutics and theoretical formulations. Nasca et al. (1) point out the need to further validate their findings and the association with treatment-refractory females with a history of early adversity. Most importantly, well-controlled clinical therapeutic studies of LAC in depression and TRD and its correlates would be an excellent first step. In addition, assessment of LAC levels in patients with bipolar disorder could be of considerable import, especially since childhood adversity is a risk factor for early-onset bipolar disorder and a more difficult and treatment-resistant subsequent course of illness (3).

It should be pointed out that among the preliminary clinical studies and reviews of LAC that Nasca et al. (1) cited was the suggestion of better tolerability of LAC compared with other ADs, and a more rapid onset of effect compared with fluoxetine in dysthymic elderly patients (4). Thus, it is possible that, as with findings in the preclinical models, LAC will exert rapid-acting AD effects clinically. This is noteworthy as several other rapid-acting ADs, such as ketamine, have effects in modulating glutamate (blocking NMDA receptors and increasing AMPA receptors) and increasing BDNF. Interestingly, lamotrigine, as well as carbamazepine, decrease glutamate release and also appear to have AD effects but of the slower-onset variety, nonetheless further suggesting that decreasing excess synaptic glutamate is associated with AD effects (5–7). *N*-Acetylcysteine, which has a slow onset of AD effects (8), increases glutamate transporters, clearing glutamate into glial cells (6, 7, 9). Thus, LAC may take its place among the three other AD modalities that decrease synaptic glutamate, but doing this in a unique way based on rapid-onset epigenetic effects on increasing the transcription of inhibitory metabotropic mGluR2 receptors.

The decreases in LAC induced in animals are of particular interest, as chronic, uncontrollable, and defeat stress are also considered models for PTSD. Childhood trauma has pleomorphic effects in increasing incidence or early age of onset of multiple psychiatric and medical

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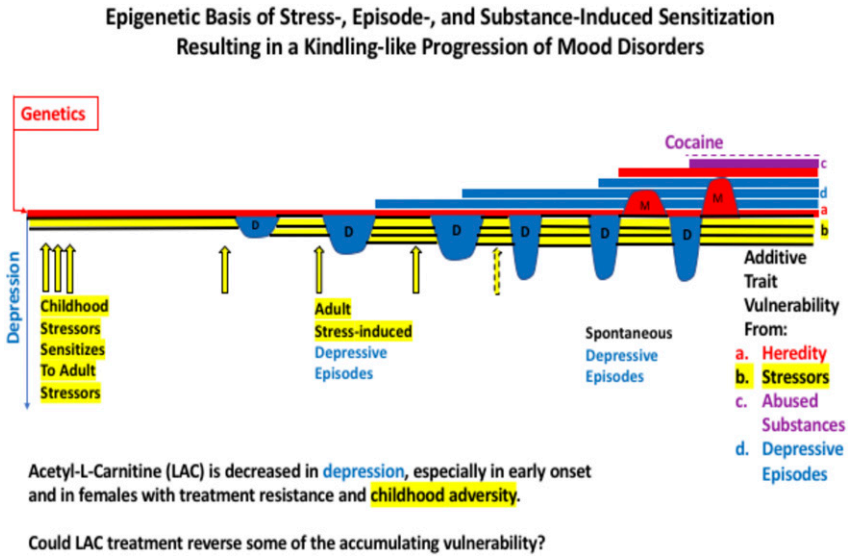


**Fig. 1. Depression as a progressive illness. When do low levels of acetyl-L-carnitine emerge in the evolution of depression?**

disorders (10, 11). If LAC decreases in humans are similarly related to childhood adversity, one could consider the possibility that treatment with LAC could have wide-ranging effects in preventing or reversing vulnerability to many illnesses.

Considerable evidence indicates that early stress can leave a vulnerability memory trace that predisposes to the development in adulthood of depression, bipolar disorder, and PTSD (6, 12–14) (Fig. 1). This memory engram appears based on epigenetic marks left on histones, DNA, and mRNA that convey sensitization (increased reactivity) to the recurrence not only of stressors but also mood episodes and bouts of substance abuse (13). There also appears to be cross-sensitization among these three types of increased reactivities, which further drive illness progression (7, 13, 15, 16). In addition, in the recurrent mood disorders, after the appearance of enough stress-induced episodes, depressions can also begin to emerge in the absence of precipitating stressors, following a kindling-like progression to spontaneous episodes (12, 13). Early-onset bipolar disorder is more prevalent in the United States compared with many European countries and runs a more difficult course, as those in the United States have more genetic vulnerability, childhood stress, affective episodes and rapid cycling, and substance abuse (3), such that earlier and new treatment interventions are desperately needed.

That LAC treatment might reverse some of the epigenetic-based vulnerability could have enormous clinical implications. In the defeat-stress model, the low BDNF in the hippocampus is related to trimethylation of H3K27 (H3K27me3) that is not reversed by traditional ADs (even though they do reverse the BDNF changes and the behavioral deficits) (17, 18). Since LAC increases acetylation of H3K27, it raises the possibility of more permanent elimination of vulnerability to defeat-stress depression-like behaviors. This proposition could readily be tested in animals and pursued clinically.

To the extent that some vulnerability to depression is based on these early childhood experiences, LAC treatment could theoretically reverse that vulnerability in the long term in a fashion different from traditional ADs, which require continued prophylactic treatment to prevent recurrent depressions (6, 14). This clinical possibility is further bolstered by the findings that LAC can induce resilience in an animal model by increasing astroglial cysteine-glutamate exchangers and glutamate transporters in the ventral hippocampus (9). LAC can also increase the structural plasticity in the medial amygdala and reverse depressive-like behaviors in a chronic restraint-stress model (19). It also has positive effects on energy balance and insulin/glucose levels, suggesting positive effects on aspects of the metabolic syndrome (20), which is so prominent in many psychiatric disorders and may be a key driver of early mortality related to cardiovascular disease (6, 14). Bigio et al. (20) concluded that "agents such as LAC that regulate metabolic factors and reduce glutamate overflow could rapidly ameliorate depression and could also be considered for treatment of insulin resistance in depressed subjects."

Nasca et al. (1) suggest that low LAC levels may be a state marker of depression since all of their patients were in a depressive episode at the time of study, but one could envision these low levels turning out to be a trait marker of either depression vulnerability or a persisting effect of a person having experienced childhood adversity. Whichever turns out to be the case, the findings of Nasca et al. (1) are clinically impactful and groundbreaking. They also hold the possibility of heralding a new era of biological markers, personalized medicine, and paradigm-shifting acute and preventative treatments at the level of epigenetics.


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