

## *Drug Review*

# Current Status of use of Acetyl-L-Carnitine in Neuropsychiatry

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Acetyl-L-carnitine (ALC) is the acetyl ester of L-carnitine, a fundamental compound that plays an essential role in the metabolism of fatty acids in mitochondria. In mammalian tissues, L-acetyl-carnitine is synthesized from the amino acid carnitine by the enzyme carnitine acetyltransferase (CRAT). Exogenously administered ALC is transported into the brain through an active transport mediated by a high affinity organic cation/carnitine transporter (OCTN2) that is functionally expressed in the blood-brain barrier of mammals.<sup>1</sup>

It has been studied across different neuropsychiatric conditions. These include depression, fibromyalgia, fatigue, male infertility and sexual dysfunction, Alzheimer's disease, alcohol abuse and ADHD. The current article aims at presenting a brief overview of the current status of its role in these conditions.

### **Depression**

Previous study shows that alterations of fatty acids and lipid metabolism occur in depression. Low cholesterol levels are associated with higher prevalence of depressive symptoms and risk for suicide.<sup>2</sup> It has been hypothesized that depressive illness is due to an alteration in membrane molecular dynamics. The alteration in membrane structure results in altered function of membrane proteins, such as receptors. The antidepressant activity of ALC is hypothesized to be due to their effect on membrane phospholipid metabolism. Such a mechanism could affect the secretion of hormones, cytokines and prostaglandins, all suggested being played a role in occurrence of depression.<sup>3</sup>

### **Clinical trials of ALC in Depression**

Table 1 summarizes the studies exploring the

role of ALC in depression.

### **Fibromyalgia**

One double-blind, multicenter trial comparing acetyl- l-carnitine with placebo in the treatment of fibromyalgia patients shows statistically significant between-group difference for depression and musculo-skeletal pain. Significantly larger improvements in SF36 questionnaire were observed in ALC than in placebo group for most parameters.<sup>8</sup>

### **Fatigue**

Abnormal mitochondria have been observed in muscle of some elderly with fatigue, suggesting some underlying abnormalities in muscle mitochondrial energy production. Recent studies found biochemical and genetic characteristics in CFS patients, such as a decreased concentration of serum acetyl-L-carnitine, a serotonin-transporter gene-promoter polymorphism, and autoantibodies against the muscarinic cholinergic receptor.<sup>9</sup>

ALC facilitate uptake of acetyl CoA into the mitochondria during fatty acid oxidation and is helpful for cellular energy supply. It stimulates protein and membrane cardiolipin synthesis which help in proper membrane orientation of mitochondria. Also, it enhances acetylcholine production helps in increasing physical activity.

### **Clinical trial of ALC in Fatigue**

Table 2 summarizes the studies exploring the role of ALC in fatigue.

### **Male Fertility and Sexual Function**

ALC causes improvement in sexual dysfunction, depressed mood, and fatigue associated with male aging. One RCT shows that carnitine is significantly more active than testosterone in

**Table 1: Studies exploring role of ALC in depressive disorder**

<b>Trials</b>	<b>Methods</b>	<b>Participants</b>	<b>Interventions</b>	<b>Result</b>
Tempesta et al. (1987) <sup>4</sup>	A cross over study vs placebo	24 hospitalized geriatric patients of major depression	Half the patients received ALC for 1 month and placebo thereafter, the other half received placebo and acetyl-carnitine thereafter	Acetylcarnitine was particularly effective in patients showing more serious clinical symptoms
Garzya et al (1990) <sup>5</sup>	Randomised placebo controlled study	28 geriatric patients of major depression	500 mg three times a day of L-acetylcarnitine tablet or placebo	LAC is effective in counteracting symptoms of depression (improvement in HRSD, BDI score)
Bella et al, (1990) <sup>6</sup>	Randomised placebo controlled study	60 senile patients with DSM-III diagnosis of dysthymia	3 gm/d LAC or placebo HRSD, BDI measured at 30days,60days	LAC group shows significant reduction in the severity of depressive symptoms (p<0.002), a significant improvement (p < 0.0027) in QOL
Zanardi& Smeraldi, (2006) <sup>7</sup>	Double-blind, randomised, controlled clinical trial	204 patients of dysthymia	ALC 500 mg b.i.d. or amisulpride 50 mg u.i.d. in a double-blind study, for 12 weeks.	ALC is as effective as amisulpride in dysthymia, less withdrawal rate

**Table 2: Studies exploring role of ALC in fatigue**

<b>Trials</b>	<b>Methods</b>	<b>Participants</b>	<b>Interventions</b>	<b>Result</b>
Tomassini et al, (2004) <sup>10</sup>	Randomised, double-blind, crossover trial	36 MS patients presenting with fatigue	Either amantadine (100 mg twice daily) or ALC (1 g twice daily) for 3 months. After 3-month washout period, they crossed over to alternative treatment for 3 month	ALC is better tolerated and more effective than amantadine for the treatment of MS-related fatigue
Malaguarnera et al, (2008) <sup>11</sup>	Open label trial	96 aged subjects of C.F.S.	500 mg three times a day of L-acetylcarnitine (LAC) tablet for 12 weeks	Decrease of physical fatigue, mental fatigue, improvements in functional status and cognitive functions
Vermeuln & Scholte, (2004) <sup>12</sup>	Open, randomized trial	30 chronic fatigue syndrome patients	2 g/d acetyl-L-carnitine, 2 g/d propionyl-L-carnitine, and its combination in 3 groups	Acetylcarnitine significantly improved mental fatigue and propionylcarnitin improved general fatigue.
Tejani et al, (2010) <sup>13</sup>	Cochrane database review			Insufficient evidence for the treatment of MS-related fatigue

improving nocturnal penile tumescence and International Index of Erectile Function score.<sup>14</sup> Acetylcarnitine plus propionyl-L-carnitine improve efficacy of sildenafil in treatment of erectile dysfunction after bilateral nerve-sparing radical retropubic prostatectomy.<sup>15</sup> ALCAR is more

effective than tamoxifen in the therapy of acute and early chronic Peyronie's disease thereby causing improvement in associated sexual dysfunction.<sup>16</sup> A Placebo-controlled double-blind randomized trial on the use of L-carnitine, L-acetylcarnitine, or combined in men with idiopathic astheno-

zoospermia shows sperm cell motility increased in patients to whom acetylcarnitine was administered both alone or in combination with carnitine.<sup>17</sup>

### Alcohol Abuse

One randomized, double-blind, placebo-controlled, pilot study in 64 alcohol-dependent anhedonic patients suggest that ALCAR can reduce craving and the time to first drink.<sup>18</sup> Another multicentred double-blind placebo-controlled study reported acetyl-L-carnitine can be a useful and safe therapeutic agent in the subtle cognitive disturbances of chronic alcoholics.<sup>19</sup>

### ADHD

Treatment with carnitine has shown to significantly decrease the attention problems and aggressive behavior in boys with ADHD. ALC has been found to be significantly superior ( $p = 0.02$ ) to placebo in the inattentive sub-type of ADHD.<sup>20</sup> L-acetylcarnitine may help with attention deficit hyperactivity disorder in children with fragile X syndrome.<sup>21</sup>

### Alzheimer's Disease

Acetyl-L-Carnitine is shown to increase membrane stability by altering cell membrane dynamics. ALC treatment causes restoration of synaptic function thereby prevents excessive

neuronal cell death. ALC has a neuromodulatory effect on neuronal cholinergic and GABAergic neurons. Chronic administration of ALC in experimental animal showed facilitation in the number and density of synapses. ALC increases choline uptake into nerve terminals, which would increase acetylcholine synthesis.<sup>22</sup>

Table 3 summarizes the studies exploring the role of ALC in Alzheimer's disease.

### Dosage and Administration

The recommended dosage range of Acetyl-L-Carnitine is from 500-1500mgs daily. It is given two to three divided oral doses.

### Conclusion

There is limited evidence for use of ALC in various neuropsychiatric disorders. It has not been studied in comparative trials involving psychotropic medications already indicated for these conditions. There is a need to conduct comparative trials before role of ALC in these conditions becomes clearly established.

### References

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**Table 3: Studies exploring role of ALC in Alzheimer's Disease**

Trials	Methods	Participants	Interventions	Result
Passeri et al, (1990) <sup>23</sup>	Randomised, double-blind, placebo controlled study	60 patients aged over 65 years, suffering from mild mental impairment	One group patients underwent therapy with acetyl-L-carnitine, 2 g/day for 3 months, other group was received a placebo.	ALC group showed significant improvement in behavioral scales, memory tests, attention barrage test, Verbal Fluency test
Bianchetti et al, (2003) <sup>24</sup>	Open label trial	23 patients with mild AD who had not responded to AChE-I	ALC (2 g/day orally for 3 months) in association with donepezil or rivastigmine	The response rate (38% after AChE-I) increased to 50% in cognitive functions, functional status, behavioral symp.
Montgomery et al, (2003) <sup>25</sup>	Meta-analysis	21 RCT in MCI and/or mild AD identified 1204 subjects (591 received ALC and 613 placebo).	Dosing was 1.5 to 3.0 g/d	Significant benefit in MCI and mild AD. ALC provided more benefit for memory & higher cognitive functions
Hudson & Tabet, (2003) <sup>26</sup>	Cochrane Database Systemic Review	Sixteen studies for inclusion		No overall benefit for ALC in clinical severity, daily activities, or cognitive measures

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