

INTEGRATED HEALTHCARE PRACTITIONERS

Integrated Healthcare Practitioners' Dietary and Nutritional
Supplement, and Herbal Remedies Management Program

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SUCCESSFUL COMPLETION OF THE QUESTIONS AT THE END OF THIS PAPER HAS BEEN APPROVED FOR CONTINUING
EDUCATION BY THE BDDT-N; 0.5 CREDIT PHARMACOLOGY, 0.5 CREDIT NUTRITIONAL MEDICINE AND BY THE
CNPBC; ONE CE HOUR.

Acetyl-L-Carnitine

Clinical application as a neuroprotective agent

INTRODUCTION

As an essential regulator of mitochondrial function and fatty acid metabolism, L-carnitine is relatively well known for its ability to improve muscle function in conditions such as cardiac ischemia, and is often used in the treatment of other muscular conditions such as fibromyalgia. The ability of carnitine to impact neurological function, however, is perhaps less well known. Surprisingly, there is a fairly well developed corpus around the use of acetyl-L-carnitine (ALC) in patients with neurological conditions ranging from age related dementia, substance withdrawal, depression, Down syndrome, attention deficient hyperactivity disorder, neuropathy, and encephalopathy secondary to liver failure (Arnold 2007, Janiri 2009, Malaguarnera 2008, Montgomery 2003, Pueschel 2006, Youle 2007, Zanardi 2006). This paper reviews the neuroprotective effects of ALC, with a narrowed focus on its effects in Alzheimer's disease (AD), substance withdrawal, and toxic peripheral neuropathies.

PHYSIOLOGY

As reviewed previously, carnitine is a key factor in the transport of fatty acids between the cytoplasm and the mitochondria, facilitating production of ATP, and appears to be in especially high demand under ischemic conditions. Acetyl-L-carnitine passes the blood-brain barrier through an active transport process and is highly concentrated in the brain, especially in the hypothalamus (Thal 2000, Virmani 2004), and is therefore the main focus of carnitine research in the area of neurological disease.

ALC exerts its neuroprotective effect through a variety of mechanisms. According to Quatraro, ALC has analgesic effects by acutely increasing blood levels of the endogenous opioid

peptide beta-endorphin, neurotropic effects by upregulating nerve growth factor receptors on the brain and preventing accumulation of lipofuscin, and metabolic effects by increasing the oxidative metabolism of neurons (Calvani 1992, Quatraro 1995). Pettegrew used magnetic resonance spectroscopy to show that administration of ALC normalized brain levels of high energy phosphates in patients with AD compared to healthy controls (1995). ALC also has antioxidant effects, increasing glutathione and decreasing malondialdehyde (Thal 2000). Finally, acetyl-L-carnitine is thought to have cholinergic effects through facilitation of intracellular acetylcholine synthesis; carnitine transports acetyl groups out of the mitochondria into the cytoplasm where they can be used for ACh production (Thal 2000, Virmani 2004).

CLINICAL EVIDENCE: COGNITIVE IMPAIRMENT AND/OR ALZHEIMER'S DISEASE

ALC has been shown to improve cognitive function in elderly patients without dementia. Two randomized double blind placebo controlled trials showed ALC to improve mental fatigue in patients over 70 and over 100 years of age, respectively, along with concomitant improvements in physical function

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(Malaguarnera 2008, 2007). A third trial reported significant improvements in cognitive function, memory, emotional affect, and mood when evaluated in 481 elderly patients without AD (Salvioli 1994).

Two meta analyses have evaluated the effect of ALC for use in AD and/ or mild cognitive impairment (MCI) (Hudson 2003, Montgomery 2003). Montgomery included 21 randomized double blind placebo controlled trials assessing ALC for AD or MCI and concluded that ACL should be considered for the treatment of these conditions (2003). Doses ranged from 1.5 to 3.0 g/d for between 3 to 12 months. A combined effect size was calculated that incorporated both clinical and psychometric outcomes from the trials. There was significant benefit from treatment with ALC compared to placebo, effect size ES 0.201 (95% CI 0.107-0.295), and there was also a significant effect in the pooled Clinical Global Impression of Change, ES 0.32 (95% CI 0.18-0.47). ALC was well tolerated (Montgomery 2003).

The Cochrane review updated in 2008 included 16 randomized double blind placebo controlled trials (Hudson 2003). By contrast, this analysis found that while there was a statistically significant treatment effect in favour of ALC on the Clinical Global

Impression at 12 and 24 wk (OR 1.90, 95% CI 1.31-2.76 and OR 2.33, 95% CI 1.31-4.14 respectively) this was not sustained at 52 weeks (OR 0.91, 95% CI 0.58-1.43). Similar effects were seen in pooled results for the Mini Mental State Exam (MMSE), leading authors to conclude that ALC may be of limited benefit.

This review excluded several studies that were included by Montgomery on the basis of poor reporting and/ or trial design. These trials were largely earlier trials out of Italy, so poor reporting standards may be to blame. In any case, the consequent discrepancy in included studies partially explains the divergent conclusions reached by the two studies. In addition, Montgomery utilized a unique composite effect measure that may not be directly comparable to those used by Hudson by pooling data across different assessment scales. However, it seems that the possibility of ALC benefiting at least a subset of patients with Alzheimer's or MCI should not be ruled out. Hudson explains that the mechanisms by which ALC is absorbed and metabolized in the gut and liver "suggest that a large inter-individual variability should be expected in the general population. Studies have not taken this into account in selecting the dose of ALC, and this may be a source of error" (2003). Select trials of ALC for cognitive impairment are summarized in Table 1.

Table 1. Controlled Trials of Acetyl-L-Carnitine for Alzheimer's or Cognitive Impairment

Design	Outcomes	Ref
RDBPCT; n=229 patients with early onset AD ALC 3g/d x 1y	ALC did not slow the progression of AD in the overall study population as assessed by the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) and the Clinical Dementia Rating Scale (CDR). Among subjects who completed the study, there was less deterioration in the MMSE for the ALC-treated subjects, but there was no difference in rate of decline on the CIBIC and the ADL scale. There was a 25 and 24% attrition rate among the placebo and ALC groups respectively. Lack of significant findings may also be explained in part by the slower than expected rate of decline among the group as a whole.	Thal 2000
RDBPCT; n=334 young patients with AD ALC 3g/d x 1y	Reanalysis of Thal 1996 using a "trilinear approach," a model that tries to account for periods of disease stability as well as deterioration when assessing the effect of treatment on disease change. The ALC and the placebo groups exhibited the same mean rate of change on the ADAS (0.68 points/month). However, multiple regression analysis demonstrated a statistically significant Age x Drug interaction that showed that younger subjects benefited more from ALC, with significant benefit for those under the age of 61 years. Overall, both groups declined at the same rate on all primary and most secondary measures during the trial, however a subanalysis by age that compared early-onset patients (aged 65 years or younger at study entry) with late-onset patients (older than 66 at study entry), found a trend to slowed disease among patients <65 yoa receiving ALC.	Brooks 1998 Thal 1996
DBPCT; n=12 AD patients and 21 healthy controls ALC 3g/d x1y	At 12 months ALC-treated patients showed significantly less deterioration in their MMS (p=0.01) and ADAS scores compared to AD patients on placebo. At 6mo, patients on placebo has worsened significantly compared to baseline according to the ADAS (p=0.01), but not patients on ALC. pMRS showed that there was a significant increase in brain levels of phosphomonoesters at 6 months compared to baseline (p =0.03) in the ALC group but not the placebo group.	Pettegrew 1995

SBPC x-over trial; n=481 elderly subjects without AD ALC 1.5g/d x90d	There were significant improvements in the following after ALC: Cognitive function as assessed by MMSE ($p < 0.0001$); Memory as assessed by the Randt Memory Test, and this effect persisted even after ALC was discontinued; Emotional-affective area (mood, depression) as assessed by GDS and the Hamilton Rating Scale ($p < 0.0001$); Behavioural-relational aspects (instability, negative feeling) as evaluated by the Family Stress Scale ($p < 0.0004$).	Salvioli 1994 [Abstr]
RDBPCT; n=30 AD patients ALC 2.5g/d x3mo then 3g/d x3mo	After 6 months, the acetyl levocarnitine group demonstrated significantly less deterioration in timed cancellation tasks and Digit Span (forward) and a trend toward less deterioration in a timed verbal fluency task. No differences were found in any other neuropsychological test results. A subgroup with the lowest baseline scores and receiving ALC had significantly less deterioration on the verbal memory test and a concomitant significant increase in cerebrospinal fluid ALC levels compared the placebo group.	Sano 1992
RDBPCT; n=130 AD patients ALC x1y	After 1 year, both the treated and placebo groups worsened, but the treated group showed a slower rate of deterioration in 13 of the 14 outcome measures, reaching statistical significance for the Blessed Dementia Scale, logical intelligence, ideomotor and buccofacial apraxia, and selective attention. After adjustments, the treated group showed better scores on all outcome measures and this reached statistical significance for the Blessed Dementia Scale, logical intelligence, verbal critical abilities, long-term verbal memory, and selective attention.	Spagnoli 1991 [Abstr]
PC x-over trial; n=236 patients with mild age related dementia ALC 1.5g/d x150d	Multivariate analysis showed that ALC treatment “significantly increased the effectiveness of performance on all the measures of cognitive functioning and of emotional-affective state and on some scores of the relational behavior.”	Cipolli 1990 [Abstr] Neri 1990 [Abstr]
RDBPCT; n=36 AD patients ALC 2g/d x 24wk	There were no significant difference between groups, however, there was a trend for more improvement in the ALC group in relation to the Names Learning Test and a computerized Digit Recall Test, measures of short-term memory, as well less deterioration of reaction time in the computerized classification in the ALC group. Changes failed to reach statistical significance in part due to the small number of patients available for analysis. 5 patients in the ALC group experienced nausea and vomiting.	Rai 1990
RDBPCT; n=30 patients with mild dementia ALC 2g/d x 3mo	The ALC treated patients showed significant improvement in: behavioural performance (Blessed Dementia Scale $p < 0.02$; Stuard Hospital Geriatric Rating Scale $p < 0.01$); memory tests ($p < 0.02$); attention testing ($p < 0.01$); the Verbal Fluency test $p < 0.01$).	Passeri 1990, 1988 [Abstr]
DBPCT; n=40 “senile” patients ALC 1.5g/d x40d	“Statistical analysis of results confirmed that short-term, intensive L-acetylcarnitine treatment can determine a significant improvement of the main mental parameters of the senile brain, without incidence of significant side effects.”	Bonavita 1986 [Abstr]
<p>Key: AD Alzheimer’s disease; ADAS Alzheimer’s Disease Assessment Scale; ADL Activities of Daily Living scale; ALC acetyl-L-carnitine; CIBIC Clinician-Based Impression of Change; GDS Geriatric depression scale; MCI mild cognitive impairment; MMSE Mini Mental Status Exam; NR not reported; OR odds ratio; PC placebo controlled; RDBPCT randomized double blind placebo controlled trial; SB single blind; x-over cross over trial</p>		

One uncontrolled trial found that the addition of ALC to the treatment of acetylcholinesterase inhibitor resistant patients with AD increased the response rate from 38% to 50% (p value not given) (Bianchetti 2003). ALC may therefore be useful for augmenting the effect of other therapies, even when it is not sufficient as a stand alone intervention.

SUBSTANCE WITHDRAWAL

A handful of trials have examined the potential effectiveness

of ALC in ameliorating the symptoms of withdrawal from substances including methadone, cocaine, and alcohol. Janiri 2009 found that oral ALC 2g/d significantly decreased symptoms of methadone (opiate) withdrawal compared to placebo in 30 patients undergoing a three week detoxification program. Total symptom scores during the first five days were significantly lower in the ALC group ($p < 0.05$), and in particular the following symptoms were improved: muscle tension and muscle spasm ($p < 0.05$), insomnia ($p < 0.005$), and feelings of

coldness ($p < 0.05$). Pain as assessed by the Huskisson analog scale was also “considerably lower” in the ALC group from after week one until the end of the study.

One study found no impact on symptoms of cocaine withdrawal or drug cravings (Reid 2005), while two RCTs reported significant improvements in cognitive impairment, mood, and anhedonia associated with chronic alcohol abuse in abstinent patients (Martinotti 2011, Tempesta 1990).

PERIPHERAL NEUROPATHY

ALC appears to protect nerves from the effects of toxic drugs such as antiretroviral therapy and chemotherapy, and from the damaging effects of diabetes. One RCT and three open trials have reported improvements in pain and/ or symptom scores from administration of ALC in patients with antiretroviral toxic neuropathy (Hart 2004, Osio 2006, Scarpini 1997, Youle 2007). Two open trials have found reductions in neuropathy grade and/ or symptomatic improvements in patients with

neuropathy of chemotherapy (Bianchi 2005, Maestri 2005). Four RCTs and one open trial reported improvements in pain and/ or neuropathy grade when ALC was given to patients with diabetes (De Grandis 2002, Quatraro 1995, Sima 2005). These studies are summarized in Table 2.

ALC has been shown to aid in the regeneration of damaged nerve tissue. Hart found that on biopsy, the skin of patients taking ALC for six months showed significant increases in the number of small sensory fibers, a 133% increase in the dermis, and 100% in the epidermis (2004). Furthermore, epidermal innervation reached up to 92% of that compared to healthy HIV- controls without neuropathy (Hart 2004). Sima demonstrated similar results in diabetic patients (2005). ALC has also been shown to improve of nerve conduction parameters, velocity and amplitude (Bianchi 2005, De Grandis 2002). Sima reported no effect on this outcome (2005), while Uzun found improvement in those patients with stage 1a diabetic neuropathy, but not those with stage 1b disease (2005).

Table 2. Neuroprotective Properties of ALC in Human Trials

Design	Outcomes	Ref
Antiretroviral Toxic Neuropathy		
RDBPCT+ open label; n=90 HIV+ pt w distal polyneuropathy. ALC 1g/d IM x14d, then 2g/d orally x42d	<ul style="list-style-type: none"> No change in pain according to ITT analysis, but there was significant improvement in per protocol analysis in the ALC group c/t placebo after 14d (IM injections), $p < 0.022$. During the open label phase (oral administration), there was improvement in the Visual analog scale, Total symptom score, and McGill Pain Questionnaire in all. 	Youle 2007
Open trial; n=20 HIV+ patients with ATN. ALC 2g/d x4wk	<ul style="list-style-type: none"> Mean pain intensity score was significantly reduced from 7.35 at baseline to 5.80 at week 4 ($p = 0.0001$). No change in electrophysiological parameters during the 4wk. “well tolerated.” 	Osio 2006
Open trial; n=21 HIV+ patients with ATN and HIV-controls without neuropathy. ALC 3g/d x 33 mo	<ul style="list-style-type: none"> After 6 months, skin biopsy of the leg showed that small sensory fibres had increased (epidermis 100%, $P = 0.006$; dermis 133%, $P < 0.05$). Epidermal, dermal and sweat gland innervation reached 92%, 80% and 69% c/t controls. Improvements continued or stabilized after 24 month's treatment. Neuropathic grade improved in 76% of patients and remained unchanged in 19%. 	Hart 2004
Open trial; n=16 HIV+ patients with ATN. ALC 0.5-1.0 g/d IM or IV x3wk	<ul style="list-style-type: none"> Ten patients (62.5%) reported an improvement of symptoms, five patients (31.25%) were unchanged, one patient worsened. 	Scarpini 1997
Chemotherapy (Paclitaxel/ Cisplatin) Induced Neuropathy		
Open trial; n=25 patients with grade 3 neuropathy secondary to chemo ALC 3g/d x8wk	<ul style="list-style-type: none"> 24 of 25 patients reported symptomatic relief: sensory neuropathy grade improved in 15 of 25 patients (60%), and motor neuropathy improved in 11 of 14 (79%). Objective tests of nerve function improved (sensory amplitude and conduction velocity). Symptomatic improvement persisted for a median 13 months after treatment with ALC in 12 of 13 patients. 2 patients reported mild nausea. 	Bianchi 2005

Open trial; n=27 patients with chemo-induced neuropathy. ALC 1g/d IV x10d	<ul style="list-style-type: none"> • At least one grade improvement in the peripheral neuropathy severity was seen in 73% of patients. • One case of insomnia related to ALC treatment was reported. 	Maestri 2005 [Abstr]
Diabetic Neuropathy		
Open trial; n=51 children with type 1 DM + 21 healthy controls. ALC 2g/m2/d x2mo	<ul style="list-style-type: none"> • Stage 1a patients (abnormal nerve conduction study but neurologic exam normal) had a 44% improvement in all pathologic nerve conduction parameters and a 50% improvement in sympathetic skin responses; • Stage 1 b patients (nerve conduction and neurologic examination pathologic) had similar improvement in skin responses, but no improvement was seen in nerve conduction parameters. 	Uzun 2005 [Abstr]
Analysis of 2 RPBCTs: n=1257 patients w type 1 or 2 DM. ALC 1.5 or 3.0 g/d x52wk	<ul style="list-style-type: none"> • Nerve biopsies showed a significant increase in all biopsy parameters in the ALC group, including increased nerve fibre number, and increase in regenerating clusters. (p<0.05 for all). Significant improvement in vibration perception. • No change in nerve conduction. • Pain improved significantly in those patients taking 3g/d dose (p=0.031 and p=0.025). Improved paresthesias (p=0.09) and dizziness (p=0.03) in some patients. 	Sima 2005
RDBPCT; n=333 patients ALC 1g/d x10d, then 2g/d x 355d	Among the 294 patients with impaired electrophysiological parameters at baseline, those treated with LAC showed a significant improvement in mean nerve conduction velocity and amplitude compared with placebo (p < 0.01). Mean VAS scores for pain at 12 mo were significantly reduced from baseline by 39% in LAC-treated patients (p < 0.0 vs baseline) c/t 8% in the placebo group.	DeGrandis 2002
RSBPC x-over trial; n=20 diabetic patients. ALC 0.5 g/d IM x15d	VAS of neuropathy symptoms improved significantly with ALC (p<0.001). No change in vibration perception.	Quatraro 1995
Key: ALC acetyl-L-carnitine; ATN antiretroviral toxic neuropathy; c/t compared to; DM diabetes mellitus; IM intramuscular; ITT intention to treat; IV intravenous; pt patients; RDBPCT randomized double blind placebo controlled trial		

CEREBROVASCULAR INSUFFICIENCY

Finally, two small controlled trials have examined ALC in patients with cerebrovascular insufficiency (Arrigo 1990, Postiglione 1991). Intravenous administration of a single dose of ALC 1.5g increased cerebral blood flow compared to placebo (p<0.05) to the ischemic area but not the area corresponding to the stroke among 20 patients with a history of ischemic stroke when assessed by single proton emission computed tomography (SPECT) imaging (Postiglione 1991, Abstr). A cross over study in 12 patients undergoing rehab for cerebrovascular insufficiency reported that “significant differences between the drug [ALC] and placebo were found in memory, number and word tests and in the responses to simple stimuli and the performance of the maze test” (Arrigo 1990, Abstr).

CONCLUSION

Acetyl-L-carnitine possesses analgesic, neuroprotective,

metabolic, and cholinergic activities. Human studies have demonstrated clinical improvements associated with ALC use in a range of neurological conditions including Alzheimer’s disease and age related cognitive impairment, psychological and cognitive effects of chronic alcohol abuse, methadone withdrawal, toxic neuropathy of various etiologies, and chronic cerebrovascular insufficiency. Although there is some question as to the consistency of its effects between individual patients especially in AD, the majority of the evidence suggests that acetyl-L-carnitine would be a valuable intervention for use in the treatment of toxic or degenerative neurological conditions where permitted by jurisdiction of practice.

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Questions

1. Which of the following is true about the mechanism of action of acetyl-L-carnitine (ALC)?
 - a) It is able to cross the blood brain barrier and concentrates in the hypothalamus
 - b) Can normalize levels of high energy phosphates in the brain of patients with Alzheimer's disease (AD)
 - c) Facilitates synthesis of acetylcholine
 - d) All of the above

2. Meta analyses by Montgomery (2003) and Hudson (2003) have yielded conflicting results. Possible reasons for this include:
 - a) Montgomery used a unique composite effect measure that is not directly comparable to the measures assessed by Hudson
 - b) Montgomery includes a wider selection of studies including earlier Italian trials excluded by Hudson on the basis of reporting quality
 - c) Hudson's review was published by Cochrane, which is known to be extremely conservative in conclusions endorsed
 - d) All of the above

3. Montgomery's meta analysis found that there was significant benefit from use of ALC on clinical and psychometric parameters when used for 3-12 months, but Hudson found that this effect dissipated over time, with no significant effects persisting at 12 months.
 - a) True
 - b) False

4. One uncontrolled trial found that the addition of ALC to the treatment of acetylcholinesterase inhibitor resistant patients with AD increased the response rate from 38% to:
 - a) 45%
 - b) 48%
 - c) 50%
 - d) 58%

5. Janiri 2009 found that ALC could help alleviate symptoms of methadone withdrawal, improving which of the following symptoms?
 - a) anxiety
 - b) hot flushes
 - c) muscle tension
 - d) all of the above

6. Two studies found that ALC may be able to improve neurological symptoms of chronic alcohol abuse including:
 - a) cognitive impairment
 - b) anhedonia
 - c) mood
 - d) all of the above

7. Human trials have demonstrated that ALC can improve which types of neuropathies?
 - a) chemotherapy induced neuropathy
 - b) Bell's palsy
 - c) idiopathic neuropathy
 - d) all of the above

8. ALC has been shown to improve function in damaged nerves by:
 - a) stimulating regeneration of nerve fibres, with increased innervation in dermal and epidermal tissues
 - b) decrease nerve conduction parameters including conduction velocity and amplitude
 - c) strengthening surrounding supporting tissues such as muscle
 - d) upregulating detoxification of noxious substances

9. Proton emission computed tomography (SPECT) showed that intravenous ALC 1.5g increased cerebral blood flow compared to placebo ($p < 0.05$) to the ischemic area and the area corresponding to the stroke in stroke patients.
 - a. True
 - b. False

10. Bianchi 2005 conducted an open trial of ALC for the treatment of chemotherapy induced neuropathy. The following results were found:
 - a) 24 of 25 patients (96%) reported some form of symptomatic relief;
 - b) Sensory neuropathy grade improved in 60% and motor neuropathy improved in 79%;
 - c) Objective tests of nerve function - sensory amplitude and conduction velocity – improved compared to baseline;
 - d) All of the above.

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