

Issue 230

In a nutshell

Many RCTs have tested acetyl-L-carnitine (ALC) in Alzheimer's disease and mild dementia.

The best interpretation of the collective trial data is that this therapy shows promising but not as yet definitive results, whilst others interpret much the same data as amounting to an equivocal outcome. Since it appears to be safe, we believe ALC is a treatment worth trying in appropriate patients.

Carnitine for Alzheimer's disease

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Carnitine is essential for energy production in cell mitochondria (red structures)



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NUTRITION RESEARCH REVIEW

Study 1: Meta-analysis finds benefit

A meta-analysis was conducted on randomised, placebo-controlled trials of acetyl-L-carnitine (ALC) over at least 3 months duration in patients with mild cognitive impairment or mild Alzheimer's disease.

Subjects: A total of 21 RCTs with 1,204 subjects, average age 72 years, with doses of 1.5-3.0 gm/day over anywhere between 3 and 12 months.

Results: In 17/21 studies the effect on the combination of all measures used was positive for ALC vs placebo, and the combined effect size for all measures in all studies was 0.20 (95% CI: 0.11-0.30). 'Objective' and subjective measures were highly correlated ($r=0.9$).

Although there were some side-effects (e.g. GIT discomfort, insomnia etc.), these were not significantly more in active than placebo groups and ALC was generally well tolerated. See Graph.

Reference: Montgomery SA. et al. Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *Int Clin Psychopharmacol.* 2003 Mar;18(2):61-71.

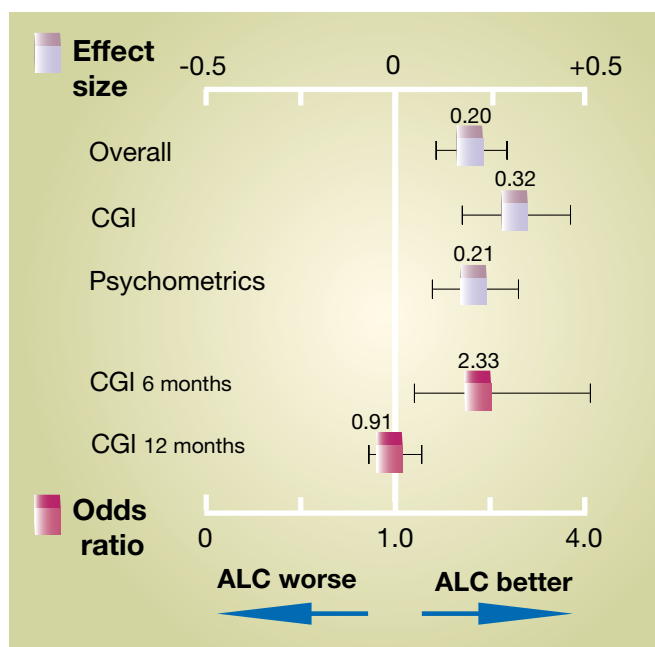
Study 2: Meta-analysis finds little benefit

Another meta-analysis considering mostly the same studies as Study 1 has found little objective evidence of benefit from ALC in Alzheimer's disease.

Subjects and method: 16 RCTs (1,843 subjects) on ALC in doses and durations similar to (meta-analysis Study 1) in patients with mild to moderate cognitive decline or Alzheimer's disease.

Graph: Meta-analyses of RCTs acetyl-L-carnitine vs placebo in Alzheimer's disease

(Study 1 results shown as lighter bars in top portion, Study 2 results are darker bars in lower portion of graph).



Results: Comparing ALC with placebo, there was a significant benefit at 6 months in Mini Mental State examination ($p=0.02$) and clinical global impression (CGI) (dicotomous: improved vs not improved, $p<0.05$) but not at 1 year, nor in CGI as a continuous measure, dementia severity, or functional ability. See Graph.

Reference: Hudson S. et al. Acetyl-L-carnitine for dementia. *Cochrane Database Syst Rev.* 2003;(2):CD003158.

Comments

For those who believe that a meta-analysis of RCTs is the best way to sort out what is evidence-based clinical practice from what is not, the above two papers present a curious challenge.

The two sets of authors looked at pretty much the same RCTs (19/21 trials in Study 1 were reviewed for the second paper), yet came to apparently very different conclusions:

Study 1: "The positive effect...suggests that [ALC] should be considered for treatment..." vs

Study 2: "No evidence of benefit...for dementia".

What accounts for this difference, and what should clinicians deduce about the value of ALC in dementia?

One clear point of difference between the papers lies in which trials the authors considered suitable to use in their formal meta-analysis. Study 2 excluded a number of RCTs that appeared in Study 1's statistics, whilst including one trial that was not in Study 1.

The focus of the analyses was also different, for example Study 1 combined all the varying time frames (although they also report a mixed effect of time on the various outcomes), whereas Study 2 breaks them down by duration. Time specific analysis no doubt gives a better feel for the persistence of any effect. But if it means less subject numbers within each time frame this will reduce the power of the analysis to show any real effect that may be present.

Both papers point out the difficulties in combining RCTs published over a wide time span (20 years) in which methodologies for assessment of the status of dementia have changed. That assessment remains a rather imprecise matter even now.

It is also important to consider what patient population is being considered - particularly the age and severity of dementia at baseline. A re-analysis of an already published multi-centre RCT, for example, found that, whilst the original paper had failed to demonstrate a significant ALC effect ¹, there was an impact when only younger (<61 years) patients were considered ². But a later RCT on just such younger patients by the same research group found little benefit, other than a small drop in the rate of decline of mental state score ³.

What is perhaps surprising is just how many RCTs have actually been done on this topic. Presumably the logic behind this interest is the unique function of carnitine in facilitating fatty acid transfer into and the production of energy within mitochondria, its ease of entry into the brain and its role in the synthesis of the neurotransmitter acetylcholine ⁴ (for more

detail see our previous issues #212 and #101). Some have postulated that carnitine might help delay the "mitochondrial decay of aging" ⁵ and there is animal evidence of it protecting against neurotoxicity ⁶. Carnitine acetyltransferase activity was reported to be decreased in Alzheimer's patients ⁷, though carnitine levels in their CSF were not different from controls ⁸.

Carnitine has also been used in other psychiatric and neurological conditions, such as drug-induced peripheral neuropathy ⁹, depression in aging men ^{10, 11}, fatigue in multiple sclerosis and the elderly ^{12, 13}, early age-related macular degeneration (in combination with other antioxidants) ¹⁴ and in memory loss in alcoholics ¹⁵. These were, however, mostly small trials not so far confirmed by further studies.

So where does this leave us with Alzheimer's disease? Frankly, the finer statistical and methodological differences between the two meta-analyses are hard to resolve. It seems to us that, on the basis of the present evidence, acetyl-L-carnitine is well worth trying in Alzheimer's patients, particularly in the earlier stages. The RCT evidence can at best be described as promising, and at worst equivocal. Fortunately there seems little evidence thus far of safety problems.

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