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L-carnitine for cognitive enhancement in people without cognitive impairment (Protocol)

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[Intervention Protocol]

L-carnitine for cognitive enhancement in people without cognitive impairment

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy and safety of L-carnitine for the enhancement of cognitive function in people without cognitive impairment.

BACKGROUND

Description of the condition

Cognitive functions, such as attention, perception, memory, and language, are crucial for human functioning. People use these capacities to process information, including acquiring, selecting, representing and retaining relevant data and using them to guide behaviours (Sanberg 2006). Evidence from long-term follow-up studies and systematic reviews suggests an inverse association between early-life cognitive function and adult risk of unintentional injury and mortality (Calvin 2011; Osler 2007). With the continuous development of society, better cognition also is considered to mean stronger social adaptability and higher living quality (Clark 2014; Eickenhorst 2012; Franke 2011). Therefore, the maintenance and improvement of cognitive function has been gradually gaining attention from people in modern society and many people are interested in dietary supplements or drugs which might enhance cognition (Clark 2014; Deline 2014; Eickenhorst 2012). Cognitive enhancement has been defined as the amplification or extension of one or more core capacities of the mind, thus improving people's information processing systems and allowing them to achieve better performance in their daily life (McKendrick 2014; Sanberg 2006). Safe interventions which could enhance cognitive function in people would be very valuable.

Description of the intervention

L-carnitine (the enantiomeric form of carnitine) is a quaternary ammonium compound synthesised from the amino acids lysine or methionine. It is an important contributor to cellular energy metabolism. Although discovered in 1905, the crucial role of L-carnitine in metabolism was not elucidated until 1955, and its deficiency was not described until 1972 (Kelly 1998; Bhattacharyya 1995). The most significant source of L-carnitine in the human diet is meat, and humans also can synthesise L-carnitine from dietary amino acids. It is produced in the liver and kidneys and stored mainly in the most active metabolic tissue such as the skeletal

muscles, heart, brain, and sperm. The plasma concentration of L-carnitine varies with age, increasing until nearly 70 years old, then tending to diminish in parallel with the reduction in body mass index and muscle mass (Malaguarnera 1999). Acetyl-L-carnitine (ALC) and propionyl-L-carnitine (PLC) are the most important naturally-occurring carnitine derivatives. The body can convert L-carnitine to ALC or PLC and vice versa. Therefore, theoretically L-carnitine and its natural derivatives may play some similar roles in the body, but because of their chemical structures they appear to possess different strengths in some specific tissues (Malaguarnera 2012; Mingorance 2011).

Although L-carnitine is supplied exogenously and can be synthesised endogenously, both primary and secondary deficiencies do occur. Carnitine deficiency can be acquired or can be a result of inborn errors of metabolism (Stanley 2004). Pre-term infants are at risk for carnitine deficiency due to impaired synthesis and insufficient renal tubular resorption (Evangeliou 2003). Secondary carnitine deficiency is more common and is usually associated with dialysis in chronic renal failure, although it can also be induced by intestinal resection, severe infection, and liver disease.

Besides being found in certain foods (e.g. meats, dairy products and some plants), L-carnitine is also available as supplements or included in some mixed products, such as energy drinks and vitamin mixtures. Currently, at least four formulations of L-carnitine supplements are available - liquid, tablet, capsule and powder - and sometimes it is supplied as one component in a multi-component preparation or a dietary intervention (Lcarnitine 2015). Oral supplementation of L-carnitine in individual dosages greater than 2g appears to offer no advantage, since the mucosal absorption of carnitine appears to be saturated at about a 2g dose (Harper 1988). Maximum blood concentration is reached approximately 3.5 hours after an oral dose and slowly decreases, with a half-life of about 15 hours (Bach 1983). Elimination of carnitine occurs primarily through the kidneys (Bach 1983).

Possible side effects of L-carnitine have been reported, including agitation, headache, diarrhoea, nausea, vomiting, anorexia and abdominal discomfort, mostly of mild or moderate severity (Hudson 2003; Montgomery 2003; Wang 2014).

L-carnitine and its derivatives have been proposed as a treatment, or as an adjunct to conventional medicine, for many conditions, including stable angina, intermittent claudication, diabetic neuropathy, kidney disease and dialysis, hyperthyroidism, male infertility, erectile dysfunction, chronic fatigue syndrome, Alzheimer's disease and memory impairment (Hudson 2003; Montgomery 2003; Ribas 2014; Shang 2014; Wang 2014). ALC is thought to traverse the blood-brain barrier more readily and may have a preferential effect on the central nervous system, whereas PLC may have better bioavailability and be specific for skeletal and cardiac muscle (Malaguarnera 2012; Mingorance 2011).

How the intervention might work

L-carnitine is involved in energy production

L-carnitine is a cofactor required for transformation of free long-chain fatty acids into acylcarnitines, and for their subsequent transport into the mitochondrial matrix, where they undergo beta-oxidation for cellular energy production. Increasing L-carnitine content might increase the rate of fatty acid oxidation, permitting a reduction of glucose utilisation, preserving muscle glycogen content, and ensuring maximal rates of oxidative ATP production (Brass 1994a; Brass 1994b; Brass 1994c).

Improvement of cognitive function may be connected to processes influenced by the brain's energy production

In brain tissue, the L-carnitine shuttle mediates translocation of the acetyl moiety from mitochondria into the cytosol and thus contributes to the synthesis of acetylcholine and of acetylcarnitine (Montgomery 2003; Naleczz 1996). ALC can traverse the blood-brain barrier and modulate phospholipid metabolism, synaptic morphology, and synaptic transmission, and can enhance the synthesis and release of cellular macromolecules (such as neurotrophic factors, neurohormones and multiple neurotransmitters) (Benton 2004; Pettegrew 2000; Virmani 2004), which may be helpful to improve cognitive function.

Why it is important to do this review

To ensure better quality of life and professional success, maintaining and improving cognitive function has won people's attention day by day. L-carnitine is a cognitive enhancing agent which might be supplied as a nutritional aid, and it has already been reported to enhance cognitive function in subjects (Hudson 2003; Montgomery 2003; Spagnoli 1991). However, it is not approved for such effects in people without cognitive impairment and the evidence has not as yet been reviewed systematically. This systematic review of efficacy and safety aims to guide clinical practice and to inform consumer choice.

OBJECTIVES

To assess the efficacy and safety of L-carnitine for the enhancement of cognitive function in people without cognitive impairment.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised or quasi-randomised controlled trials (RCTs) in which L-carnitine or its derivatives (acetyl-L-carnitine (ALC) or propionyl-L-carnitine (PLC)) are given with the intention of enhancing cognitive function and are compared with a placebo or no-treatment control group. Trials may have a parallel group or cross-over design.

Types of participants

People with intact cognition of any age and either gender are eligible. Participants should have no self-reported history or evidence of neurologic and psychiatric disorders, and they should achieve normal scores when assessed by any acceptable cognitive tests.
We will exclude patients with a diagnosis of mild cognitive impairment (MCI) or dementia caused by any kind of disorders (e.g. Alzheimer's Disease), or other significant illnesses associated with cognitive impairment (such as schizophrenia, depression or generalised anxiety disorder). Patients with known carnitine deficiency will also be excluded. However, patients with illnesses or disorders of other systems (e.g. diabetes mellitus, hypertension) but without existing cognitive impairment will be included.

Types of interventions

Active intervention: L-carnitine and its derivative, ALC or PLC, irrespective of formulation, dose or duration of treatment. We will not include trials assessing a multi-component preparation or dietary supplement which contains L-carnitine or its derivatives.
Control intervention: placebo or no treatment.

Types of outcome measures

Primary outcomes

1. Cognitive function as measured by psychometric tests. These should be validated for use in healthy populations and may include comprehensive neuropsychological test batteries or tests of individual cognitive domains (e.g. memory functions including verbal memory, visual memory, wording memory, immediate or delayed recall, executive function, attention, etc.).
2. Incidence and severity of adverse effects.

Search methods for identification of studies

We will search for all RCTs and quasi-RCTs of L-carnitine for cognitive enhancement, without language restrictions.

Electronic searches

We will search ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's Specialised Register. The search terms will be: "L-carnitine" or "acetyl-L-carnitine" or "propionyl-L-carnitine" or "ALC" or "PLC" or "ALCAR" or "ALPAR".
ALOIS is maintained by the Trials Search Co-ordinator of the Cochrane Dementia and Cognitive Improvement Group and contains dementia and cognitive improvement studies identified from:

1. Monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and LILACS
2. Monthly searches of a number of trial registers: meta Register of Controlled Trials; Umin Japan Trial Register; WHO portal (which covers ClinicalTrials.gov; ISRCTN; Chinese Clinical Trials Register; German Clinical Trials Register; Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others)
3. Quarterly search of *The Cochrane Library*'s Central Register of Controlled trials (CENTRAL)
4. Six-monthly searches of a number of grey literature sources: ISI Web of knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses

To view a list of all sources searched for ALOIS see 'About ALOIS' on the ALOIS website.
We will run additional separate searches in many of the above sources to ensure that studies involving participants without cognitive impairment are identified and that the most up-to-date results are retrieved. The MEDLINE search strategy can be seen in Appendix 1.

Searching other resources

We will check the references of published studies to identify additional trials. We will also review the bibliographies of the RCTs identified, and contact the authors to identify additional published or unpublished data if possible.

Data collection and analysis

Selection of studies

Two review authors (Muke Zhou and Ning Chen) will independently scrutinise titles and abstracts identified from the register search. These two authors will obtain the full text of all potentially-relevant studies for independent assessment, and then decide which trials fit the inclusion criteria. When there are disagreements about inclusion criteria, the two authors will discuss the discrepancy carefully. A third review author (Li He) will help to arbitrate if agreement cannot be reached.

Data extraction and management

Two authors (Muke Zhou and Ning Chen) will independently extract data from the trials to complete a data extraction form. The form includes the study name, type of design, study population size, duration, number of participant withdrawals, participants analysed in the different treatment groups, inclusion and exclusion criteria, intervention (route and dosage), and outcomes. One author (Muke Zhou) will enter data into Review Manager software (RevMan 5) and a second author (Ning Chen) will check the data entry.

Assessment of risk of bias in included studies

The assessment of risk of bias will take into account the method of random sequence generation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and any other potential sources of bias. Two authors (Ning Chen and Muke Zhou) will assess these items independently according to The Cochrane Collaboration's standard scheme (Higgins 2011c). Then we will judge all trials for each item and categorise them as follows:

A. Low risk of bias for all key domains: low risk of bias.

B. Unclear risk of bias for one or more key domains: unclear risk of bias.

C. High risk of bias for one or more key domains: high risk of bias.

According to the method of assessing risk of bias in cross-over trials (Higgins 2011c), we will evaluate the following items for included cross-over trials: (i) whether the cross-over design is suitable; (ii) whether there is a carry-over effect (the washout period should be no shorter than five half-life durations of each intervention); (iii) whether only first period data are available; (iv) incorrect analysis; and (v) comparability of results with those from parallel-group trials.

Measures of treatment effect

We will analyse data using RevMan 5 software. We will calculate a weighted treatment effect using a fixed-effect model across trials unless there is substantial heterogeneity, in which case we will use a random-effects model. We will express results as risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes and as mean differences (MDs) or standardised mean differences (SMDs) for continuous outcomes.

Unit of analysis issues

We will include only studies randomising individuals. We will include cross-over trials as long as either first-period data or data taking account of the cross-over design are available. If a study includes repeated measures of the same outcome, then we will define several outcomes based on different periods of follow-up and perform separate analyses. If studies compare more than two intervention groups, we will select the most relevant pair of intervention groups to include in the analyses (Higgins 2011b).

Dealing with missing data

1. We will contact the original investigators to request missing data whenever possible.
2. We will record the amount of missing data and reasons given. We will also record any imputation methods used by the study authors. If possible, we will include intention-to-treat data. If this is not available, then we will include per protocol data and identify them as such.
3. We will perform sensitivity analyses to assess how sensitive results are to reasonable changes in the assumptions that are made, whenever possible.
4. We will address the potential impact of missing data on the findings of the review in the Discussion section.

Assessment of heterogeneity

We will assess heterogeneity amongst trials by using the Chi^2 test. A P value of 0.10 will be used to determine statistical significance. When P is less than 0.10, it may indicate a problem with the heterogeneity of combined data. We will also use I^2 values to quantify inconsistency across studies, which reflects the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. An I^2 value between 30% to 50% may represent moderate heterogeneity, while a value above 50% suggests it is substantial (Deeks 2011; Higgins 2002; Higgins 2003). In the case of $I^2 > 30\%$ and sufficient numbers of studies (at least two for each kind of subgroup characteristic), we will conduct subgroup analyses to try to identify reasons for the heterogeneity.

Assessment of reporting biases

The within-study risk of bias from selective outcome reporting will be assessed for each included trial according to the standard described in the Assessment of risk of bias in included studies section. We will try to obtain the study protocol, and then compare outcomes in the protocol and published report. When the protocol is unavailable, we will compare outcome measures listed in the methods section with those reported in the results section. We will use funnel plots to investigate the possibility of between-study publication bias if there are sufficient numbers of included studies (at least 10 included in a meta-analysis) (Sterne 2011).

Data synthesis

Outcomes measured by the same or similar scales for global cognitive function or for individual cognitive domains may be pooled in one meta-analysis. If studies assess outcomes at different times, we will perform separate analyses for the following time points:

after a single dose, latest time point up to and including 4 weeks, latest time point after 4 weeks.

If we consider that all studies in a meta-analysis are estimating the same underlying treatment effect, then we will use a fixed-effect model, otherwise we will use a random-effects model. We will also undertake descriptive analyses of other included trials (Higgins 2011a).

Subgroup analysis and investigation of heterogeneity

We will carry out subgroup analyses to explore potential sources of heterogeneity, including different derivative forms (e.g. l-carnitine, ALC and PLC) and nature of control intervention (placebo or no treatment). We will also perform a subgroup analysis of studies including younger patients (aged less than 60 years) if possible.

Sensitivity analysis

A sensitivity analysis will be conducted after excluding studies at a high risk of bias assessed by the methods mentioned above. We will also consider a sensitivity analysis when we identify some issues potentially leading to arbitrary or contentious results during the review process.

We will perform sensitivity analysis to assess how sensitive results are to reasonable changes in the assumptions made for imputing missing data. If sensitivity analyses do not change the overall findings and conclusions greatly, the results of the review will be regarded with a higher degree of certainty. Otherwise, the conclusions will be considered uncertain, and we will try to contact trial authors and obtain individual patient data for further analyses. If this cannot be achieved, we will interpret the results with caution (Deeks 2011).

'Summary of findings' table

We will present the results of our meta-analyses in a 'Summary of findings' (SoF) table, based on the methods described in chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We will include the following outcomes in the SoF table: global cognitive function, memory, executive function, and adverse effects. For each outcome, we will present an estimate of the effect size, the quantity of data contributing to the estimate and our level of confidence in the estimate based on the GRADE criteria of imprecision, inconsistency between studies, risk of bias, indirectness and publication bias (Schünemann 2011).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. L-carnitine.ti,ab.
2. Carnitine/
3. (ALC or PLC or ALCAR or ALPAR).ti,ab.
4. "acetyl-l-carnitine".ti,ab.
5. "propionyl-l-carnitine".mp.
6. or/1-5
7. randomized controlled trial.pt.
8. controlled clinical trial.pt.
9. randomi?ed.ab.
10. placebo.ab.
11. drug therapy.fs.
12. randomly.ab.
13. trial.ab.
14. groups.ab.
15. or/7-14
16. (animals not (humans and animals)).sh.
17. 15 not 16
18. 6 and 17
19. (cognit* or memory or mental or brain).ti,ab.
20. dement*.ti,ab.
21. alzheimer*.ti,ab.

22. exp Dementia/ or exp Cognition/
23. (healthy or older or elder* or aged).ti,ab.
24. Aged/
25. seniors.ti,ab.
26. or/19-25
27. 18 and 26

WHAT'S NEW

Date	Event	Description
29 October 2015	New citation required and major changes	The title was changed and the protocol (Yang 2011) was extensively revised.

CONTRIBUTIONS OF AUTHORS

Ning Chen and Mi Yang: wrote the draft of protocol and will write the review.

Muke Zhou, Ning Chen, Jian Guo, Jing Xiao: will perform data collection, methodological quality assessment and analyses.

Li He: the corresponding author, developed the proposal, offered expert advice, reviewed the protocol, and is responsible for developing and updating the review.

DECLARATIONS OF INTEREST

Ning Chen-None known

Mi Yang-None known

Muke Zhou-None known

Jing Xiao-None known

Jian Guo-None known

Li He-None known

Ruxin Xing-None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

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NOTES

The protocol was first published in Issue 11, 2011 of *The Cochrane Library* (Yang 2011) but the title and types of participants have been changed in the updated protocol to make the objectives of the review clearer.