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[Intervention Review]

L-acetylcarnitine for treating fragile X syndrome

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ABSTRACT

Background

People with fragile X syndrome (FXS) have an intellectual dysfunction that can range from very mild to severe. Symptoms can include speech and language delays and behavioural difficulties such as aggression or self injurious behaviours, emotional lability, and anxiety-related problems (for example obsessive-compulsive symptoms and perseverative behaviours). In some cases, affected people may have an additional diagnosis of attention deficit hyperactivity disorder or an autism spectrum disorder.

Objectives

To review the efficacy and safety of L-acetylcarnitine in improving the psychological, intellectual, and social performance of people with FXS.

Search methods

In May 2015 we searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, Web of Science, and two other databases. We also searched three trials registers, four theses databases, and the reference lists of relevant studies and reviews.

Selection criteria

Randomised controlled trials (RCTs) that assessed the efficacy of L-acetylcarnitine, at any dose, in people of any age diagnosed with FXS compared with placebo.

Data collection and analysis

For each trial, two review authors independently extracted data on the children included and interventions compared, and assessed the risk of bias of the studies across the following domains: randomisation sequence generation, allocation concealment, blinding (of participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other potential sources of bias.

Main results

We found only two RCTs that compared oral L-acetylcarnitine (LAC) with oral placebo in children with FXS. The studies included a total of 83 participants, all of them male, who were treated and followed for one year. The age of participants at the start of treatment ranged from 6 to 13 years, with a mean age of 9 years. Neither study provided information on randomisation, allocation concealment procedures, or



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blinding of outcome assessment, and we received no responses from the authors we emailed for clarification. We therefore rated studies as being at unclear risk of bias on these domains. We judged both studies to be at low risk of bias for blinding of participants and personnel, incomplete outcome data, and selective reporting, but to be at high risk of other bias, as at least one study was funded by a drug company, and in both studies people working for the company were part of the research team.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the quality of the available evidence. Overall, the quality of the evidence was low due to the imprecision of results and high risk of other bias.

Regarding the primary outcome of psychological and learning capabilities, both studies assessed the effect of interventions on children's verbal and non-verbal intellectual functioning using the Wechsler Intelligence Scale for Children - Revised. The authors did not provide detailed data on those results but said that they found no important differences between treatment and placebo.

Both studies evaluated the impact of the treatment on hyperactive behaviour using the Conners' Abbreviated Parent-Teacher Questionnaire. In one study, teachers' assessments of the children found no clear evidence of a difference (mean difference (MD) 0.50, 95% confidence interval (CI) -5.08 to 6.08, n = 51; low-quality evidence). The other study stated that there were no differences between treated and untreated participants, but did not provide detailed data for inclusion in the meta-analysis.

Parents' assessments favoured LAC in one study (MD -0.57, 95% CI -0.94 to -0.19, n = 17; low-quality evidence), but not in the other (MD -2.80, 95% CI -7.61 to 2.01, n = 51; low-quality evidence), though changes were not large enough to be considered clinically relevant.

Regarding social skills, one study reported no clear evidence of a difference in Vineland Adaptive Behavior composite scores (MD 8.20, 95% CI -0.02 to 16.42, n = 51; low-quality evidence), yet results in the socialisation domain favoured LAC (MD 11.30, 95% CI 2.52 to 20.08, n = 51; low-quality evidence).

Both studies assessed the safety of the active treatment and recorded no side effects. Neither of the included studies assessed the secondary outcome of caregiver burden.

Authors' conclusions

Low-quality evidence from two small trials showed that when compared to placebo, LAC may not improve intellectual functioning or hyperactive behaviour in children with FXS.

PLAIN LANGUAGE SUMMARY

Is L-acetylcarnitine an effective treatment for fragile X syndrome?

Review question We wanted to know the efficacy and safety of L-acetylcarnitine (LAC) as compared to placebo in people with fragile X syndrome.

Background People with fragile X syndrome have intellectual impairments that can range from very mild to severe. Symptoms can include speech and language delays, and in some cases, affected people can present with behavioural problems associated with attention deficit hyperactivity disorder or autism spectrum disorder.

Study characteristics We searched the scientific literature for all randomised trials published up to May 2015 and found only two trials to include in the review. The trials recruited a total of 83 boys (6 to 13 years of age) who were treated for a maximum of one year.

Key results We found no clear evidence of important differences in verbal and non-verbal intellectual functioning between treatment with LAC and placebo.

Regarding hyperactive behaviour, teachers' assessments found no clear evidence of differences between treatment with LAC and placebo. Parents' assessments showed some differences between treatments favouring LAC, but changes were not large enough to be considered clinically relevant.

Only one study assessed social skills, and it reported no clear evidence of a difference between LAC and placebo in adaptive behaviour, though results in the socialisation domain favoured LAC.

No side effects were reported, and no study reported on the secondary outcome of caregiver burden.

Quality of the evidence The available evidence is of low quality. Risk of bias for these studies is unclear regarding the procedures used to randomise participants to LAC or placebo, to conceal treatment allocation, and to blind assessors to the results of the treatments.

Funding of the studies At least one of the studies was funded by a drug manufacturer with a commercial interest in the results. One of the studies was also funded by charitable monies.

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