Systematic review of pharmacological treatments in fragile X syndrome

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CRD summary
This review assessed the efficacy and safety of pharmacotherapy in treating fragile X syndrome and concluded that there was no robust evidence to recommend any type of pharmacotherapy. The review was generally well-conducted and the conclusion appears reliable given the limited evidence available.

Authors' objectives
To systematically review the evidence on the efficacy and safety of pharmacotherapy in the treatment of people with fragile X syndrome.

Searching
PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and other Cochrane Library databases were searched until March 2009. No language restrictions were applied. Search terms were specified. Reference lists of retrieved articles were searched.

Study selection
Clinical controlled trials (CCTs) were included if they: compared at least one pharmacological treatment with placebo or another treatment; included people diagnosed with fragile X syndrome (FXS); assessed either efficacy and/or safety of the treatment; and included main outcome results that measured psychological and social performance using standardised or validated scales. Trials were excluded if they assessed the impact of treatments in people in fragile X pre-mutation related conditions.

Where reported, almost all trials were placebo-controlled, most participants were male, age ranged from one to 49 years and IQ (intelligence quotient) ranged from 21 to 77. Many participants were classified as autistic or with attentional problems such as attention deficit hyperactivity disorder. Treatments included folic acid (dose range 5mg/day to 250mg/day), ampakine compound CX516 (600mg/day to 900mg/day), dextroamphetamine (2mg/kg/day) and methylphenidate (0.6mg/kg/day) and L-acetylcarnitine (20mg/kg/day to 100mg/kg/day).

Two reviewers performed the study selection.

Assessment of study quality
Two reviewers independently assessed the quality of trials using Cochrane Collaboration criteria in terms of: allocation sequence generation; allocation concealment; blinding; incomplete outcome data; and selective outcome reporting. Disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted outcome data. Data were measured using standardised and validated instruments related to intelligence and behavioural, emotional and learning capabilities. Data were largely extracted in terms of direction of change; few numerical data were available.

Methods of synthesis
A narrative synthesis was used. Results were reported by treatment type.

Results of the review
Fourteen studies (n=229 participants, range=2 to 63) were included in the review. Length of follow-up ranged from 16 days to 12 months.

Ten trials assessed folic acid (n=82 participants; comprising eight crossover, one parallel group and one unreported design), six of which were randomised, only one reported adequate sequence generation and blinding, and none reported adequate concealment. Two trials (n=83 participants) assessed L-acetylcarnitine. Both trials used parallel...
randomised study designs, although neither reported adequate sequence generation, concealment or blinding. One trial assessed ampakine compound CX516 (n=49 participants). This trial reported adequate sequence generation, concealment and blinding. One trial assessed dextroamphetamine and methylphenidate (n=15 participants) and reported adequate blinding, but not concealment or sequence generation.

**Folic acid**: Ten studies assessed efficacy and safety of folic acid. Only one trial (n=25 participants; the highest quality trial of the 10) reported a statistically significant difference in outcomes between treatment and placebo groups (a statistically significant improvement in IQ scores favoured the treatment group). Most trials did not report any statistical testing. Only one trial reported side effects (transient problems with diarrhoea, sleep delays and mood swings).

**L-acetylcarnitine**: One trial reported a statistically significant reduction in hyperactive behaviour in the L-acetylcarnitine group using the Conners' abbreviated parent questionnaire. One trial reported statistically significant differences between groups, which favoured L-acetylcarnitine using Conners' global index-parents (CGI-P) and Vineland adaptive behaviour (VAB) scale. No side effects were reported.

**Ampakine compound CX516**: One trial (n=49 participants) reported no statistically significant difference in outcomes between treatment and placebo groups. Minimal side effects, which included allergic rashes, were reported in the treatment group.

**Dextroamphetamine and methylphenidate**: One trial found both dextroamphetamine and methylphenidate to be associated with a statistically significant improvement in the attention deficit and hyperactivity disorder comprehensive teacher's rating scale (ACTeRS). Side effects reported included mood lability and irritability.

**Authors' conclusions**
There was no robust evidence to support recommendations on pharmacological treatments in patients with fragile X syndrome either in general or in those with additional diagnosis of attention deficit and hyperactivity disorder or autism.

**CRD commentary**
The research question was clear regarding the subsequent analyses of treatment efficacy and safety in relation to impairments associated with FXS. Inclusion criteria were clear. The authors searched a number of relevant sources with adequate attempts to minimise language bias. It was unclear whether unpublished studies were sought, so publication bias could not be ruled out. Trial validity was assessed and reported clearly. Sufficient details of the primary studies were provided, although there were some inconsistencies between results as tabulated and as included in the body of text. Use of a narrative synthesis seemed appropriate given clinical heterogeneity between trials. Most trials were very small and of unclear quality, and so their results may not have been reliable. The review was generally well-conducted, with sufficient attempts made to minimise errors and biases. The cautious conclusion seems reliable given the available evidence.

**Implications of the review for practice and research**
**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that positive results should be confirmed by properly designed and adequately powered, parallel randomised trials. New trials should include women and test whether pharmacological treatments had additional benefits if administered at a younger age.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.