Add-on therapy with acetylcholinesterase inhibitors for memory dysfunction in schizophrenia: a systematic quantitative review, part 2
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CRD summary
This review investigated the clinical use of add-on acetylcholinesterase inhibitors donepezil, rivastigmine and galantamine to improve memory performance in schizophrenia. The authors concluded that there was no clear evidence on whether acetylcholinesterase inhibitors should be prescribed for memory enhancement in patients with schizophrenia. There were several methodological issues with the review that suggested the authors' conclusions may not be reliable.

Authors' objectives
To investigate the clinical use of add-on donepezil, rivastigmine and galantamine to improve memory performance in people with schizophrenia.

Searching
The following databases were searched: PubMed (from inception), PsycINFO (1967 to 2005), EMBASE (1980 to 2005) and ISI Web of Science (for conference proceedings abstracts) (1979 to 2005). No language restrictions were applied. Search terms were reported. Additionally, reference lists were searched and researchers contacted for unpublished data. Update searches were performed in PubMed until the review was submitted.

Study selection
Randomised controlled trials (RCTs) of patients with schizophrenia-spectrum disorder who were taking any of the acetylcholinesterase inhibitors, and were tested for cognitive function with validated published rating scales for schizophrenia, were eligible for inclusion. Included RCTs had to be double blind, placebo controlled, crossover or open in design. Case studies, letters, correspondence and reviews were excluded. Trials of monotherapy, patients with disorders other than schizophrenia, post-mortem/genetic/molecular studies and conference reviews were excluded. To be included, the clinical outcome memory performance had to be included in the aggregation of effect estimate. Trials that did not adequately examine clinical outcomes were excluded.

The included studies were mainly placebo controlled and double blinded RCTs but other designs were also included, including a case series; they ranged from six to 24 weeks in duration. In the included studies, patients took the acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine (doses ranging from 3 to 10 mg/day) in addition to an antipsychotic drug (a variety of typical and atypical antipsychotics were included). A number of memory scales were included that tested short-term memory and/or long-term memory.

The authors did not state how the papers were selected for the review.

Assessment of study quality
Methodological quality of the studies was determined using the Cochrane review checklist which assessed allocation concealment, blinding (participant, investigator and outcome assessment), intention-to-treat analysis and follow-up. The authors assigned a point to each criterion

Validity was assessed by two independent reviewers and disagreements resolved by consensus.

Data extraction
Means, standard deviations and sample sizes were used to calculate effects where available.

Two reviewers independently extracted data and disagreements were resolved by consensus.
Methods of synthesis
Explicit and implicit memory tasks were pooled to derive the effect size using Hedge g for long-term memory. The short-term memory effect was derived by pooling tasks relating to visuo-spatial, auditory input, phonological loop and central executive of working memory components. Studies were pooled using fixed-effect and random-effects models and 95% confidence intervals were calculated for effect sizes. Statistical heterogeneity was assessed using the Cochrane Q statistic. Primary analysis included all studies with pre- and post-clinical data. Secondary analysis was based on double-blind, placebo-controlled, two arm designs.

Results of the review
10 studies were included in the review (n=447 patients); five placebo controlled RCTs (all double blind and one crossover trial, n=356 patients), one placebo controlled trial (double blind, n=36 patients), one crossover randomised study (n=22 patients), two open label studies (n=27 patients) and one case series (n=5 patients). Sample sizes ranged from five to 251.

Long-term memory: There was a statistically significant increase in long-term memory (eight studies) at the end of acetylcholinesterase inhibitor treatment compared with before treatment (effect size 0.362, 95% confidence interval (CI): 0.0617 to 0.663, p=0.019). When individual acetylcholinesterase inhibitors were analysed this remained significant for donepezil (five studies) but not rivastigmine (two studies) or galantamine (one study).

Short-term memory: There was no significant difference in short-term memory (nine studies). Similar results were seen with the random-effect and fixed-effects models. However, when individual acetylcholinesterase inhibitors were analysed there was a significant increase in short-term memory with donepezil (effect size 0.246, 95% CI: 0.182 to 0.780; p=0.034, four studies) but not rivastigmine (four studies) or galantamine (one study).

There was no evidence of a significant difference in either short-term memory or long-term memory when control and intervention groups were compared at the end point, this remained non-significant when results of the double blinded, placebo controlled studies only were pooled.

There was no evidence of statistically significant heterogeneity.

Further analyses were reported in the paper.

Authors’ conclusions
No clear evidence was provided on whether acetylcholinesterase inhibitors should be prescribed for memory enhancement in patients with schizophrenia, but there appeared to be a small improvement in long-term memory and short-term memory with these medications.

CRD commentary
The inclusion criteria appeared wider than the objectives of the review and were unclear with regard to intervention and study design. The authors searched for published and unpublished data in all languages, reducing the possibility of publication and language bias. Validity of the included studies was assessed but the results were not shown; it was unclear how the authors took this into account in their analysis. Validity assessment and data extraction were performed by two reviewers, reducing the risk of reviewer bias and error. However, the process of study selection was not described, so it was not known if similar steps were taken. The studies were combined in a meta-analysis and assessment of statistical heterogeneity suggested that the studies were statistically similar enough to synthesise. However, as the primary studies assessed a variety of memory scales and antipsychotics (the doses of which were unknown), and one of the studies provided more than 50% of the total patients, it cannot be ascertained that the results of the synthesis were reliable. The authors’ conclusions may therefore not be reliable.

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

Research: The authors stated that more studies are needed to establish the ideal design, duration and outcomes in future studies of acetylcholinesterase inhibitors use in the treatment of schizophrenia.
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