Cholinesterase inhibitors as adjunctive therapy in patients with schizophrenia and schizoaffective disorder: a review and meta-analysis of the literature
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CRD summary
This review found only a small effect of cholinesterase inhibitors on cognitive and psychopathological symptoms in participants with schizophrenia/schizoaffective disorders. Specific cognitive deficits (memory and motor speed/attention) appeared to be responsive to treatment. The review and the included studies had quality deficits and the results should be interpreted with caution.

Authors' objectives
To assess cognitive and clinical effects of adjunctive treatment with cholinesterase inhibitors in patients with schizophrenia and schizoaffective disorders.

Searching
PubMed and EMBASE were searched for relevant articles (up to December 2008). Search terms were indicated and there was a restriction to those in English. Reference lists of included studies were searched. Unspecified conference proceedings were searched.

Study selection
Eligible studies were randomised controlled trials (RCTs) of the use of a cholinesterase inhibitor (rivastigmine, donepezil or galantamine) as an adjunctive treatment to antipsychotic therapy (typical or atypical) in participants with schizophrenia or schizoaffective disorder. Doses of antipsychotic medication had to have been stable for at least a month. Comparison was against placebo. Trials had to assess cognitive and clinical assessment using validated rating scales and data had to be available on group means and standard deviations for baseline and post-intervention cognitive and clinical tests. Cross-over trials were included if it was possible to extract first-segment data. Studies were excluded if they included patients with schizophrenia / schizoaffective disorder and comorbid dementia. Psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS) (subscales: total, positive, negative) and recording of extra-pyramidal symptoms.

Trials included in the meta-analysis had a duration of between eight and 24 weeks. Mean age of patients ranged between 25 and 50.5 years. Atypical antipsychotic drugs were used by patients in 85% of the trials; typical antipsychotic drugs were used in 31% of the trials. Almost half of the studies included patients with schizoaffective disorders. The intervention drug was donepezil in six trials, galantamine in three trials and rivastigmine in four trials. Some trials included patients with Alzheimer's disease and some included smokers (with smoking possibly interfering with the action of cholinesterase inhibitors).

One reviewer checked the references identified in the searches against the inclusion criteria.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Where required, first authors of trials were contacted for additional information. Data from neuropsychological tests were grouped into the following domains: executive function, language, memory, motor function and attention. The Trail Making test part A was used in several trials and could be analysed separately.

The authors did not state how data were extracted for the review.

Methods of synthesis
Meta-analysis of cholinesterase inhibitors versus placebo was carried out using standardised mean differences and Hedge’s correction for bias for small samples. Heterogeneity was assessed using the Q test (significance set at 0.05). A random-effects model was used where heterogeneity was present; a fixed effects model was used where heterogeneity was absent.

Results of the review
Thirteen RCTs (n=564) were included in the meta-analysis.

No significant effect of cholinesterase inhibitors was found for the outcomes of executive function (six studies, n=199), language (four studies, n=63), total PANSS (six studies, n=119) and negative PANSS (eight studies, n=377). There was a trend towards improvement in extrapyramidal symptoms with cholinesterase inhibitors (effect size -0.57, 95% CI -1.16 to -0.02, p=0.059; three studies, n=158). Patients who received cholinesterase inhibitors performed significantly faster on the Trail Making test part A (effect size -0.69, 95% CI -1.14 to -0.23, p=0.003; four studies, n=93) and showed significantly better results for memory (effect size 0.28, 95% CI 0.06 to 0.50, p=0.014; three studies, n=146). Positive symptoms on the PANSS analysis were significantly more intense with cholinesterase inhibitors (effect size 0.28, 95% CI 0.07 to 0.50, p=0.01; seven studies, n=364, more than 50% of data contributed by one study).

Statistical heterogeneity was found for the analysis of extrapyramidal symptoms and the negative PANSS subscale, but this was not further evaluated.

Authors’ conclusions
Overall, there was little effect of cholinesterase inhibitors on cognitive and psychopathological symptoms in participants with schizophrenia or schizoaffective disorders. However, specific cognitive deficits (memory and motor speed/attention) appeared to be responsive to treatment with adjunctive rivastigmine, donepezil or galantamine.

CRD commentary
This review had some limitations in quality of methodology and reporting. Appropriate inclusion criteria were defined. A small number of relevant databases were searched and some supplementary searching was carried out (although this was incompletely described). The restriction to English-language articles may have excluded relevant non-English studies. The authors acknowledged the potential for publication bias. Review methodology was incompletely described. It seemed that major steps in the process were carried out by a single reviewer. Methodological quality was not assessed. There was some confusion in the description of included and excluded studies (studies described as excluded were not included in the meta-analysis, but were described in every other aspect as though they were included). Information on individual studies was provided.

The included studies appeared generally to have been of poor quality, with small sample sizes and inadequate control and description of factors that were potential confounders of the effects of cholinesterase inhibitors (such as the primary antipsychotic drugs used and smoking behaviour). There was heterogeneity between trials both methodologically and clinically. The authors mentioned that some findings of the review should be interpreted with caution and it was unclear to what extent the authors’ conclusions follow from the available evidence and the extent to which studies described as excluded were taken into account in the conclusions.

Two authors received honoraria from pharmaceutical companies

Implications of the review for practice and research
The authors made no specific recommendations for practice.

Research: The authors stated that higher quality studies with larger samples and longer duration of follow-up were needed. These should include careful randomisation, use of homogenous sets of scales and tests to assess drug effects, and standardisation of the primary antipsychotic drugs used in the treatment of schizophrenia. Smoking should be controlled.
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