The effectiveness of donepezil for cognitive rehabilitation after traumatic brain injury: a systematic review
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CRD summary
This review determined the effectiveness and safety of donepezil for cognitive rehabilitation after traumatic brain injury and found significant evidence for a positive effect on general cognitive ability, short-term memory and attention. The authors' appropriately cautious conclusion was that the effectiveness and safety of donepezil were uncertain due to the limited evidence available.

Authors' objectives
To determine the effectiveness and safety of donepezil for cognitive rehabilitation after traumatic brain injury.

Searching
PubMed, PsycINFO and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to March 2006 for publications in any language. Grey literature and unpublished studies were accessed by contacting the manufacturer and checking available databases for ongoing trials. Search terms were not reported, but the authors stated that alternative terms for donepezil and traumatic brain injury were used.

Study selection
Any type of clinical trial of patients with traumatic brain injury who received donepezil and that included control patients was eligible for inclusion. Most comparative studies included acute rehabilitation programmes. Most noncomparative studies assessed post acute rehabilitation programmes. Some studies allowed concomitant central nervous system treatment. Primary outcomes were assessed using various different measures, but the main eligible outcomes were the results of standard cognitive tests. Safety was assessed using attrition rates and reported adverse effects. The included studies used a donepezil dose of 5mg/day to 10mg/day for a range of three weeks to 25 months. Controls included routine treatment, crossover placebo or other acetylcholinesterase inhibitors. The age of participants ranged from 13 to 76 years. Most participants were male. Traumatic brain injury severity in the included participants varied from mild to severe. Time since injury ranged from one week to 325 months; most studies were carried out more than a year after injury.

Two researchers independently screened potentially relevant articles. The selection and classification of suitable outcomes (cognitive tests) were made by consensus between two clinical psychologists and a psychiatrist.

Assessment of study quality
Appropriate quality criteria were assessed for the relevant studies and included criteria such as randomisation, blinding, power and loss to follow-up. The authors did not state how validity assessment was performed.

Data extraction
Two reviewers extracted the data independently. Disagreements were resolved by consensus.

Methods of synthesis
Effect sizes were calculated from standardised mean differences using the method described by Hedges and Olkin for small samples. It was not appropriate to combine the standardised mean differences due to methodological heterogeneity. A narrative synthesis was presented. Studies with noncomparative designs were synthesised separately from those with comparative designs, which were randomised controlled trials (RCTs) and cohort studies.

Results of the review
Fourteen relevant studies were identified: two RCTs (n=56); one pseudo-RCT cohort study (n=111); one matched cohort study (n=36); and 10 non-comparative trials (n=106). The non-comparative trials included four case reports (n=14), two single-subject studies (n=10) and four case series (n=82). Both RCTs reported double blinding and one
carried out a power analysis. When reported, attrition rates were low.

**Comparative studies (four studies):** One RCT reported a significant benefit for donepezil compared to routine treatment (effect size 0.86, 95% CI 0.18 to 1.53) using the Mini-Mental State Examination (a general cognitive measure). The second RCT reported a significant benefit for donepezil compared to placebo for general cognitive outcomes using different scales (results for individual cognitive outcomes were reported in the review and showed a significant improvement in short-term memory and attention). The two other studies showed no significant differences between treatment groups, although one study reported a possible benefit with donepezil when administered early in the rehabilitation period.

**Noncomparative studies (10 studies):** Seven of the 10 studies reported a small to moderate improvement for several cognitive outcomes following treatment with donepezil.

Adverse effects were reported in the review.

**Authors' conclusions**
The review concluded that the effectiveness of donepezil on cognitive rehabilitation after traumatic brain injury remained uncertain. This was due to the paucity of evidence available and the poor methodological quality of the studies, although there was some evidence for its efficacy. The efficacy and safety of donepezil did not appear to differ from that of other acetylcholinesterase inhibitors.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions, study design and outcomes. Articles in any language were included, which reduced the potential for language bias. Relevant databases were searched and efforts were made to access grey literature and unpublished studies, which reduced the potential that relevant articles were missed. The authors attempted to minimise bias and error during the review process for study selection and data extraction, but not for study validity. Characteristics of individual studies were reported. The authors' decision not to pool the studies in a meta-analysis was justified given the apparent differences between the studies and measurement of outcomes. Although 14 studies were identified, the total number of participants was relatively low. This and the design of most studies and their associated limitations should be taken into consideration. This was a generally well-conducted piece of research. The authors' cautious conclusions seem appropriate based on the evidence presented.

**Implications of the review for practice and research**
**Practice:** The authors stated that there may be an optimal time window for the use of donepezil in the treatment of cognitive impairment following traumatic brain injury.

**Research:** The authors stated that good quality large RCTs were needed to prove without doubt the efficacy of donepezil and other acetylcholinesterase inhibitors in the treatment of cognitive impairment following traumatic brain injury.

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