Cholinomimetic agents and neurocognitive impairment following head injury: a systematic review
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CRD summary
This review assessed the role of cholinomimetic agents in the treatment of neurocognitive impairment following head injury. Due to the methodological limitations and heterogeneity of the included studies, the authors concluded that there was insufficient evidence to support the use of these agents in practice. The authors' conclusions and recommendations for further research were likely to be reliable.

Authors' objectives
To ascertain the role of cholinomimetic agents in the long term management of neurocognitive impairment following traumatic brain injury.

Searching
MEDLINE, EMBASE and PsycINFO were searched. Search terms were reported, but search dates were not. It was unclear whether there were any language restrictions and whether unpublished studies were included. The reference lists of retrieved articles were examined for additional studies. Experts in the area and pharmaceutical companies were contacted.

Study selection
Studies of any design reporting the use of cholinomimetic agents for neurocognitive impairment after head injury (in humans) were eligible for inclusion. The authors did not specify eligible outcome measures.

Fifteen studies reported on the use of cholinesterase inhibitors, six on the use of physostigmine with or without lecithin and four on the use of CPD-choline. Duration of treatment ranged from three days to 18 months and regimens varied across studies. One study was conducted in adolescents. Severity of head injury, where reported, varied across studies. Time elapsed since injury ranged from 10 days to 16 years (not specified in seven studies). Combinations of 65 individual psychometric tests were used as outcome measures. Clinical impression with or without subjective observations were used in 10 studies.

The authors stated that one reviewer independently assessed and selected studies for inclusion in the review.

Assessment of study quality
Summary information regarding methodological limitations was provided for each included study.

The authors did not state how the validity assessment was performed.

Data extraction
Data were extracted by one author and checked by the other. If a study was reported on more than once, data were extracted from the most recent publication. The authors did not state how any disagreements were resolved.

Methods of synthesis
Studies were combined in a narrative synthesis grouped by agent used, severity of injury and time elapsed since injury. Tables were used to present summary data for each study. Overall study findings were categorised as positive, equivocal or negative. These were presented in a table grouped by agent and study design. The authors did not attempt to assess publication bias.

Results of the review
Twenty-five studies (n=575) were included in the review: five randomised controlled trials (RCTs) (n=225); nine open
Fifteen studies reported on the use of cholinesterase inhibitors. Positive findings were evident in 10 studies, negative in three and equivocal in two. Across studies, 5mg to 10mg of donepezil showed positive improvements in cognitive function. One small double blind RCT (n=18) reported significant sustained improvements in auditory and visual memory skills (using validated measures) when compared to placebo. The largest open label study (n=111) reported increased vigilance, concentration and initiation on clinical impression and subjective assessment. In one RCT (n=80) rivastigmine showed significant improvements in verbal learning and visual information processing only in a sub-group of severely impaired cases.

Six studies reported the use of physostigmine with or without lecithin. Positive findings were evident in one study, negative in two and equivocal in three. Across case reports clinical impression showed positive neurocognitive outcomes and improvements in memory, function and global outcomes. Four studies reported on the use of CDP-choline. Positive findings were evident in three studies and equivocal in one. One large single-blind RCT (n=115) showed significant improvements in Glasgow Outcome Scales and from clinical impression compared to the control group.

Further study narratives grouped by severity of head injury and time elapsed since injury were reported in the review paper.

Authors' conclusions
There was insufficient evidence to support the use of cholinomimetic agents in the treatment of neurocognitive impairment following traumatic brain injury.

CRD commentary
This review did not have clear inclusion and exclusion criteria in terms of outcome measures. The authors searched relevant databases, but did not report search dates. Efforts were made to try and identify additional studies by reviewing reference lists of relevant literature and contacting experts in the area. It was unclear whether any attempt was made to identify unpublished studies, so relevant studies may have been missed. The risk of publication bias was not assessed. It was also unclear whether language restrictions were applied, so language bias can not be ruled out. Only one reviewer assessed and selected studies for inclusion, meaning that reviewer bias and error may have been introduced. However, appropriate efforts were made to minimise reviewer bias and error at the data extraction stage. A formal assessment of methodological quality was not carried out, although some limitations of each study were reported. Given the degree of variation in terms of study design, severity of illness, time elapsed since injury, treatment regimes and outcome measures, the authors' decision to combine the studies in a narrative was appropriate. The authors discussed sources of heterogeneity and grouped studies appropriately. Given the level of evidence presented, the authors' conclusions and recommendations for further rigorous research were appropriate. However, these should be considered in the context of the methodological weaknesses of the review.

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

Research: the authors stated that there was a need for high quality large scale RCTs with well defined inclusion and exclusion criteria, particularly for severity and location of injury. There was a need for a consensus on the outcomes to measure and tools to use. Consideration should also be given to the use of real life end point measures, such as return to work, since these are more relevant indicators of improvement for patients and carers.

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Record Status
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.