A review of studies describing the use of acetyl cholinesterase inhibitors in Parkinson's disease dementia

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CRD summary
This review assessed acetyl cholinesterase inhibitors for Parkinson's disease dementia. The authors concluded that cholinesterase inhibitors have a modest effect on cognitive symptoms but little effect on neuropsychiatric symptoms, and poor tolerability may limit their utility. The lack of a description of the review methods and the use of multiple outcomes make it difficult to comment on the reliability of the conclusions.

Authors' objectives
To assess the effects of acetyl cholinesterase inhibitors in patients with Parkinson's disease dementia (PDD).

Searching
MEDLINE, PsycINFO, EMBASE and CINAHL (all from inception to December 2004) and the Cochrane Library (December 2004) were searched for studies published in English; the search terms were reported. The reference lists of identified studies were screened and relevant pharmaceutical manufacturers were contacted. Studies reported as poster presentations were excluded.

Study selection
Study designs of evaluations included in the review
Explicit inclusion criteria were not reported. Case reports were excluded.

Specific interventions included in the review
Explicit inclusion criteria were not reported. Studies of anticholinesterase inhibitors (rivastigmine, donepezil, galantamine and tacrine) were included. The duration of treatment ranged from 6 to 56 weeks.

Participants included in the review
Explicit inclusion criteria were not reported. Studies of patients with PDD were included. The criteria used to diagnose PDD or dementia included the American Psychiatric Association's DSM-IV criteria for PDD or dementia, probable PDD, cognitive impairment secondary to Parkinson's disease, the Mini Mental State Examination (MMSE) (score between 3 to 25) or MMSE dementia, and the Global Deterioration Scale dementia.

Outcomes assessed in the review
Studies that assessed cognition were eligible for inclusion. The review also assessed Parkinsonian and neuropsychiatric symptoms and adverse effects. The review focused on assessing cognition using the MMSE, neuropsychiatric symptoms using the Neuropsychiatric Inventory (NPI) and Parkinsonian symptoms using the Unified Parkinson's Disease Rating Scale (UPDRS), where these measures were reported. The included studies used a variety of other outcome measures (further details were reported).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was not formally assessed, but blinding and methods used to handle missing data were reported for the controlled trials.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, outcomes data were extracted as the mean with standard deviation for each treatment group.

Methods of synthesis
How were the studies combined?
The studies were grouped by study design and described in the text.

How were differences between studies investigated?
Differences were apparent from the text and from inspection of the tables.

Results of the review
Ten studies (n=656) were included: 3 randomised controlled trials (RCTs; n=571) and 7 open studies (n=85).

RCTs (sample size: 14 to 541).

All of the RCTs were analysed using the last-observation-carried-forward method. Two were double-blind placebo-controlled and one used a crossover design.

The largest RCT (n=541) found that, compared with placebo, rivastigmine (3 to 12 mg daily) significantly improved cognition and neuropsychiatric symptoms: the change in MMSE was 0.8 versus -0.2 with placebo (P=0.03); the decrease in Alzheimer's Disease Assessment Scale-Cognitive subscale was 2.1 versus 0.7 with placebo (P<0.001); and the change in NPI was -2.0 versus 0.0 with placebo (P=0.02). However, this RCT found no difference between treatment for Parkinsonian symptoms (change in UPDRS, P=0.83). Rivastigmine was associated with higher withdrawal rates than placebo (27.1% versus 17.9%), significantly increased nausea (29% versus 11.2%, P<0.001), vomiting (16.6% versus 1.7%, P<0.001), Parkinsonian symptoms (27.3% versus 15.6%, P=0.002) and tremor (10.2% versus 3.9%, P=0.01).

The other 2 RCTs were small crossover double-blind RCTs (n=14 and n=16, respectively). One crossover RCT (n=14) found that donepezil significantly improved cognition: the change in MMSE score at 10 weeks was 2.1 versus 0.3 with placebo (P=0.013). The other (n=16) found no significant difference between donepezil and placebo in cognition: the Dementia Rating Scale total delta score was -0.68 (95% confidence interval: -7.63, 6.82, P=0.84). Neither RCT found any statistically significant difference in Parkinsonian. Donepezil increased the mean number of adverse effects compared with placebo in both RCTs (4.2 versus 2.8 and 71.4% versus 44.4%, respectively).

Open trials (sample size from 5 to 28).
The results were mixed. Three trials showed no effect of anticholinesterase inhibitors on cognition, three showed an improvement, and the remaining trial did not use the MMSE or any standard measure.

Authors' conclusions
Cholinesterase inhibitors have a modest effect on cognitive symptoms but there was no consistent evidence of an effect on neuropsychiatric symptoms. Tolerability may limit utility.

CRD commentary
The review question lacked explicit inclusion criteria, making it difficult to determine if appropriate methods were used to ascertain the relevance of studies included in the review. Several relevant sources were searched and attempts were made to locate unpublished studies, thus limiting the possibility of publication bias. No attempts were made to minimise language bias and the restriction to English language studies might have resulted in the loss of some data. The methods used to select studies and extract the data were not described, so it is not known whether any efforts were made to reduce errors and bias. Validity was not formally assessed and only some aspects of quality were discussed.
The studies were described in the 'Results' section rather than the evidence being synthesised, although the authors presented a limited synthesis of the evidence in their discussion. Several studies reported multiple outcomes, but the effect of this on the statistical significance of the results was not discussed. The highest quality evidence appeared to come from the largest RCT with a high drop-out rate; although this supported the conclusion about limited tolerability, it provided limited evidence about efficacy. Overall, the lack of a description of the review methods and the inadequate assessment of study quality make it difficult to comment on the strength of the evidence underpinning the authors' conclusions.

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**Implications of the review for practice and research**

**Practice:** The authors stated that patients receiving anticholinesterase inhibitors should be monitored for response and adverse events.

**Research:** The authors did not state any implications for further research.

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