Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine

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CRD summary
This review concluded that the evidence base regarding the efficacy of cholinesterase inhibitors for the behavioural and psychological symptoms of dementia was limited. The cautious conclusions reflected the evidence, but should be interpreted with caution due to the possibility of missed studies, lack of details on study quality and limitations in the synthesis.

Authors' objectives
To assess the efficacy of donepezil, rivastigmine and galantamine in the treatment of behavioural and psychological symptoms of Alzheimer's disease.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for English-language studies. Search terms were reported but dates were lacking. Reference lists of relevant articles and reviews were screened.

Study selection
Randomised controlled trials (RCTs) that compared donepezil, rivastigmine or galantamine monotherapy to placebo in patients with a diagnosis of possible or probable Alzheimer's disease based on the NINCDS-ADRDA or DSM-IV criteria were eligible for inclusion. Eligible studies reported on a robust measure of global or individual behavioural or psychological symptom of dementia. Both parallel and crossover designs were eligible. Study duration had to be at least 12 weeks. Studies in people with Down's syndrome or cerebrovascular disease were excluded.

Most of the included studies were multicentre and six were multinational. Some studies recruited patients from residential care or nursing homes; in other studies patients in institutional settings (including nursing homes) were excluded. Most studies had low behavioural scores at baseline, some specified a baseline level of behavioural disturbance for inclusion and others specifically excluded patients with moderate, severe or uncontrollable behavioural disturbances. All trials included at least some patients who took other concomitant medications. Cholinomimetic or anticholinergic medications were not permitted in any of the studies. A variety of psychometric scales were used to assess outcomes. Neuropsychiatric Inventory (NPI) was the most commonly used scale.

Assessment of study quality
The authors did not assess study quality.

Data extraction
The authors did not state how or what data were extracted from the included studies.

Methods of synthesis
A narrative synthesis was presented.

Results of the review
Fourteen studies were included. Median duration was 24 weeks (range 12 to 170 weeks).

Three of nine studies (n=2,518) reported a significant beneficial effect of donepezil. Eight of these studies used NPI scores to measure symptoms and two studies reported a significant improvement in symptoms compared to placebo. One of three studies (n=2,335) reported a significant improvement in NPI scores in patients treated with galantamine compared to placebo. Neither of the two studies (n=1,257) of rivastigmine reported a significant difference compared
to placebo.

**Authors' conclusions**
The evidence base regarding the efficacy of cholinesterase inhibitors for the behavioural and psychological symptoms of dementia was limited, in part due to methodological considerations.

**CRD commentary**
The review addressed a focused question supported by clearly defined inclusion criteria. The literature search was adequate for published studies. No specific attempts were made to locate unpublished studies and the review was restricted to English-language studies and so there was a possibility of language and publication bias. Details of the review process were not reported and so it was not possible to determine whether appropriate steps were taken to minimise bias and errors. Study quality was not formally assessed and so the reliability of the included studies was unclear. Details of the included studies were summarised in tables and discussed in the text, which helped to determine the generalisability of findings. A narrative synthesis was presented. It may have been more informative to have conducted a more statistical synthesis, and possibly a meta-analysis for studies that reported outcomes using the NPI.

The authors' cautious conclusions reflected the evidence, but should be interpreted with caution due to the possibility of missed studies, lack of details on study quality and limitations in the synthesis.

**Implications of the review for practice and research**
**Practice:** The authors stated that in the absence of alternative safe and effective management options, use of cholinesterase inhibitors was an appropriate pharmacological strategy for management of behavioural and psychological symptoms of dementia.

**Research:** The authors stated that detection of differences in individual behavioural symptoms may represent the most appropriate avenue for further study.

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