Donepezil and rivastigmine in the treatment of Alzheimer's disease: a best-evidence synthesis of the published data on their efficacy and cost effectiveness

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Authors' objectives
To assess the efficacy and safety of donepezil and rivastigmine in the treatment of Alzheimer's disease (AD).

Searching
MEDLINE, HealthSTAR and PsycINFO were searched from January 1984 to May 2000; the key terms were stated. Unpublished studies and abstracts were excluded. The reference lists in identified studies were handsearched. The search was updated by searching the same databases from May 2000 to October 2001.

Study selection
Study designs of evaluations included in the review
RCTs were eligible for inclusion if they scored 5 or more on quality criteria. Open-label extension studies identified by the updated search were also included. Parallel-group and crossover RCTs were included.

Specific interventions included in the review
Studies of donepezil and rivastigmine were eligible for inclusion. The included studies administered donepezil in doses ranging from 1 to 10 mg/day and rivastigmine in doses ranging from 1 to 21/day. The duration of randomised controlled trials (RCTs) ranged from 4 to 54 weeks for donepezil and from 7 to 12 weeks for rivastigmine. Open-label extension studies followed up patients for 72 to 240 weeks in donepezil studies and for 26 weeks in the rivastigmine study.

Participants included in the review
Studies of patients with AD were included if the diagnosis of AD was made using the 1984 Institute of Neurological and Communicative Disease and Stroke-Alzheimer's Disease and Related Disorders Association diagnostic criteria. Most of the included studies were in patients with mild to moderate AD; one study was in patients with moderate to severe AD.

Outcomes assessed in the review
Studies that assessed efficacy and safety were eligible for inclusion. The included studies assessed efficacy using different measures: the cognitive subscale of the Alzheimer's disease Assessment Scale (ADAS-cog), the Clinician's Global Impression of Change (CGIC) scale, the Clinician's Interview-Based Impression of Change with caregiver input (CIBIC-plus), the number of days to clinically evident functional decline (defined in terms of the Alzheimer's Functional Assessment and Change Scale, activities of daily living and the Clinical Dementia Rating), the Gottfries-Brane-Steen scale (GBS), and Clinical Dementia Rating-Sum of Boxes (CRD-SB). In studies using the CGIC or the CIBIC-plus, scores of less than 4 or less than 5 were considered to indicate treatment success.

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 assessed and scored using the 6-item Jadad scale. Possible scores ranged from 0 (poor quality) to 8 (high quality). Only studies that scored 5 or more by each of three raters were included in the review. Three reviewers independently assessed each study identified by the original search (1984 to 2000). The reviewers were blinded to the year of publication, journal and author, but were not blinded to the drug name. One reviewer assessed the studies identified by the updated search (2000 to 2001).
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The extracted data included source of study finding, number of patients per treatment group at baseline and completion, and results. For ADAS-cog, the mean difference between baseline and the end of follow-up were calculated for each treatment group. The difference between treatment and placebo was tabulated, along with either the 95% confidence interval (CI) of the difference or the P-value.

Methods of synthesis
How were the studies combined?
The RCTs were grouped by study drug and by outcome measure and a narrative synthesis was undertaken. The open-label extension studies for each drug were discussed separately.

How were differences between studies investigated?
The results for one RCT recruiting patients with moderate to severe disease were discussed separately.

Results of the review
Nine RCTs of donepezil (n=3,250) and two RCTs of rivastigmine (n=1,424) were included. Three open-label extension studies of donepezil (n=976 patients) and one-open label extension study of rivastigmine (463 patients) were also included.

Donepezil.

ADAS-cog as the primary outcome (6 RCTs): the studies showed that donepezil 3 mg (1 RCT), 5 mg (6 RCTs) and 10 mg (3 RCTs) significantly reduced ADAS-cog scores, indicating a significant benefit compared with placebo.

Overall clinical status using the CGIC (2 RCTs) or the CIBIC-plus (4 RCTs): the studies showed that donepezil statistically significantly increased treatment success rates compared with placebo; the success rates ranged from 21 to 89% with donepezil 5 to 10 mg, and from 14 to 80% with placebo. There was no statistically significant difference in effect according to the dose of donepezil.

The one RCT in 290 patients with moderate to severe disease (included in the CIBIC-plus results above) found that patients treated with donepezil had significantly higher mean CIBIC-plus scores compared with patients treated with placebo (P<0.001).

One RCT (431 patients) showed that donepezil increased the median time till functional decline (375 days versus 208 days). Another RCT (286 patients) showed that donepezil improved the mean decline in GBS score over 52 weeks compared with placebo; the change from baseline was 7.3 (95% CI: 3.2, 11.4) with donepezil versus 13.5 (95% CI: 9.4, 17.6) with placebo.

The authors stated that adverse effects were few and generally of mild to moderate severity. The highest rate of adverse effects was 83% with donepezil compared with 80% with placebo in one RCT. The adverse effects included diarrhoea, headache and respiratory tract infection.

Open-label studies providing information on medium-term efficacy: one study (patients from 2 RCTs) found that for patients in one of the RCTs, donepezil (5 to 10 mg) improved CRD-SB scores until week 24 of the open-label study and then the scores declined.

Rivastigmine.

ADAS-cog (2 RCTs, intention-to-treat results reported): high-dose (6 to 12 mg) rivastigmine reduced cognitive decline compared with placebo (the differences compared with placebo were 3.78 and 1.60). The results for low-dose (1 to 4 mg) rivastigmine differed between RCTs; one RCT (233 patients in the rivastigmine group) found low-dose rivastigmine significantly reduced cognitive decline at 7 weeks compared with placebo (difference 1.73, P<0.05), while the other (243 patients in the rivastigmine group) found no significant difference at 12 weeks (difference 0.03).
Patients in the placebo group of the RCT showing no difference between treatments did not deteriorate immediately from baseline, whereas patients in the other RCT did.

The RCTs found similar, apparently dose-related rates of withdrawal: 15 and 14% with low-dose rivastigmine, compared with 35 and 33% with high-dose rivastigmine and 16 and 13% with placebo. Adverse effects were generally not severe. The most common adverse effects were nausea, vomiting, diarrhoea, abdominal pain and anorexia. Dizziness, headache, fatigue and malaise tended to occur only at higher drug doses.

**Cost information**
The cost-effectiveness of donepezil and rivastigmine is reported in an economic review (see Other Publications of Related Interest).

**Authors’ conclusions**
Donepezil and rivastigmine can delay cognitive deterioration for at least 6 months in patients with mild to moderate AD. After 6 months, the ADAS-cog scores for patients using these drugs are similar to those for patients receiving placebo.

**CRD commentary**
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched and the search terms were stated. The authors acknowledged that excluding unpublished material might have led to publication bias. The methods used to select the studies and extract the data were not described; hence, any efforts made to reduce errors and bias cannot be judged. Three reviewers assessed validity using established criteria and only higher quality RCTs were included for comparisons of the active drug with placebo.

Some relevant information on the included studies was tabulated, but the proportion of patients reporting specified adverse effects was not reported and it was unclear whether details of all RCTs reporting adverse effects were presented in the text of the review. A narrative review was generally appropriate given the different outcomes used in the included studies, but it was unclear why the data for ADAS-cog were not pooled. The authors discussed some of the problems with the review, such as the difficulty in drawing conclusions about the clinical benefit for studies using outcome measures that had not been assessed in terms of their responsiveness to change or their ability to detect clinically important change. However, there was no discussion as to potential reasons for the difference in results between the two RCTs of low-dose rivastigmine. The review shows that donepezil can delay cognitive decline temporarily, thus the evidence presented supports the authors’ conclusions. However, the results for rivastigmine showed a delay in decline till 12 weeks and mixed results for low-dose rivastigmine. Hence, the authors’ conclusions for rivastigmine do not appear to be supported by the evidence presented.

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

Research: The authors stated that future RCTs and phase IV studies should include an economic assessment; data on resource utilisation should be collected at baseline and during follow-up. They also stated that studies should use a uniform economic methodology to allow comparisons across studies.

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