Review: donepezil improves cognitive and global function in people with mild to moderate Alzheimer’s disease


Q Does donepezil improve cognitive and global function in people with mild to moderate Alzheimer’s disease?

METHODS

Design: Systematic review with meta-analysis.

Data sources: Studies were identified using the Eisa Inc database and from scientific literature searches (search dates not stated).

Study selection and analysis: Eligible studies were randomised controlled trials comparing donepezil versus placebo in people with mild to moderate Alzheimer’s disease (MMSE criteria). Trials were undertaken and completed by 20 December 1999. Exclusions: not stated. Data were extracted for each individual study on the efficacy and safety of donepezil. Meta-analysis was carried out using fixed and random effects models, and results were tested for statistical heterogeneity.

Outcomes: Change in cognitive status (Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-cog)); improvement in global function (Clinician’s Interview-Based Impression of Change-plus (CIBIC-plus)).

MAIN RESULTS

Ten studies met inclusion criteria (2376 participants: 821 received 5 mg/day donepezil; 662 received 10 mg/day donepezil; 893 received placebo). At 12 and 24 weeks, donepezil (5 mg/day and 10 mg/day) significantly improved cognitive and global function in people with mild to moderate Alzheimer’s disease (see http://www.ebmentalhealth.com/supplemental for table). At 24 weeks, 10 mg/day donepezil significantly improved cognitive function compared with 5 mg/day donepezil (p = 0.015). At 24 weeks, there was no significant difference between 10 mg/day donepezil and 5 mg/day donepezil in global improvement (p = 0.08). Both doses of donepezil were well tolerated. Adverse events were mainly gastrointestinal, of mild to moderate severity.

CONCLUSIONS

Donepezil significantly improves cognitive and global function compared with placebo in people with mild to moderate Alzheimer’s disease. The 10 mg/day dose significantly improves cognitive function compared with the 5 mg/day dose.

NOTES

Groups were similar for age, sex, MMSE, CDR scores at baseline. Relatively few people in the trials were aged 80 years or more.

Commentary

Whitehead et al report a meta-analysis evaluating efficacy and tolerability of donepezil. Whereas individual, randomised, placebo controlled trials have shown benefits on global and cognitive outcomes and activities of daily living with an acceptable side effect profile, a well designed meta-analysis using high quality studies provides refined estimates of the effect size of a treatment based on larger sample sizes.

This meta-analysis has several strengths. The investigators had access to the study databases allowing use of individual patient data rather than extracting a summary score from published articles. This method is thought to increase reliability.1 Access to the databases also allowed the authors to eliminate irrelevant doses of donepezil across all outcomes of interest, extract data at specified time points, and combine data on individual adverse events of interest. The authors also had access to several unpublished trials which should reduce the impact of publication bias.

The authors do not report if there were any trials found in the literature that were not included in the Eisa database. It is important to note that the AD2000 study2 was not included as it was published subsequent to data collection. The impact of excluding the AD2000 study, which did not measure outcomes the same way, is unclear. The authors do find heterogeneity when trying to combine studies with 5 mg of donepezil for the CIBIC-plus (Clinician’s Interview-Based Impression of Change-plus) analyses. Generally, if heterogeneity is present, studies cannot be combined. The Japanese studies, which did not use the 10 mg dose, show large effect sizes at the 5 mg dose and may have accounted for this heterogeneity. The impact of ethnicity was not explored.

This study shows a significant benefit on ADAS-cog (Alzheimer’s Disease Assessment Scale-Cognitive subscale) of the 10 mg dose over the 5 mg dose at 18 and 24 weeks, and supports the current clinical guidelines of pushing the dose to 10 mg if tolerated. The CIBIC-plus measurement, which includes cognitive, behavioural, activities of daily living, and general domains, was not able to show the difference between doses. The CIBIC-plus can be expected to be less sensitive to small changes in one domain and can also be influenced by adverse effects at higher doses. The analysis of adverse events confirms the presence of dose-related cholinergic effects and lack of dose-related cardiovascular events. Overall, this meta-analysis supports the efficacy of donepezil 5–10 mg up to six months of treatment. Long term effects and the translation of these effects to important outcomes such as maintaining function, improving quality of life, and delaying institutionalisation remain to be quantified.

Krista L Lancot, PhD
Associate Professor of Psychiatry and Pharmacology, University of Toronto, Scientist, Neuroscience Research Program, Director of Health Outcomes Research, HOPE Research Centre, Sunnybrook & Women’s College Health Sciences Centre
Nathan Herrmann, MD FRCCP
Professor and Head, Division of Geriatric Psychiatry, University of Toronto, Department of Psychiatry, Sunnybrook & Women’s College Health Sciences Centre

1 Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet 1993;341:418–22.

Please see http://www.ebmentalhealth.com/supplemental for additional commentary by Professor Clive Ballard.