Caregiver-specific outcomes in antidementia clinical drug trials: a systematic review and meta-analysis

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CRD summary
This review concluded that cholinesterase inhibitors have a small beneficial effect on burden and active time use for caregivers of patients with Alzheimer's disease. This was a reasonably well-conducted systematic review and the authors' conclusions are likely to be reliable. Recommendations for future research were provided.

Authors' objectives
To assess the effect of cholinesterase inhibitors on burden and active time use of caregivers of persons with Alzheimer's disease (AD).

Searching
MEDLINE, PsycINFO, EMBASE and the Cochrane Controlled Trials Register were searched from 1990 to July 2004; the search terms were reported. The searches were restricted to publications in the English language. The reference lists of identified articles were also checked, as were abstracts from relevant scientific sessions and professional society meetings. The authors contacted individual investigators and pharmaceutical companies for additional unpublished trials and to obtain handouts from presentations of interest.

Study selection
Study designs of evaluations included in the review
Prospective trials (with repeated measures) were eligible for inclusion in the review. However, only double-blind placebo-controlled randomised controlled trials (RCTs) were eligible for inclusion in the meta-analysis.

Specific interventions included in the review
Studies of cholinesterase inhibitors or N-methyl-D-aspartate receptor modulator drugs were eligible for inclusion. The majority of the included studies used drugs that had been approved by the U.S. Food and Drug Administration for the treatment of AD: donepezil was the most commonly studied drug; other drugs used were vnelacrine, galantamine, rivastigmine, metrifonate and memantine.

Participants included in the review
Studies of informal caregivers of community-dwelling patients with AD and related disorders were eligible for inclusion in the review. However, only studies of dementia of the Alzheimer's type diagnosed using the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (4th ed.), or probable or possible AD using criteria from the National Institute for Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association, were eligible for inclusion in the meta-analysis. The majority of the included studies were of patients with mild to moderate AD; other studies included patients with moderate to severe AD, vascular dementia and Parkinson's disease-related dementia. No caregiver characteristics were reported in the review.

Outcomes assessed in the review
Studies evaluating any caregiver-specific outcome were eligible for inclusion in the review. However, only studies evaluating an aspect of caregiver burden or informal care time expenditure were eligible for inclusion in the meta-analysis. Active time use was defined as the caregivers' time spent assisting patients with the performance of activities of daily living or instrumental activities of daily living. The included studies evaluated burden, time use, health care costs, psychological morbidity, and ease of use or satisfaction with treatment. A range of outcome instruments were used.

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 using a modified version of the Verhagen Delphi criteria for the assessment of RCTs, which evaluated 13 criteria relating to outcomes, randomisation, allocation concealment, similarity of the treatment groups, eligibility criteria, blinding and statistical analysis. One reviewer performed the validity assessment.

**Data extraction**
For studies eligible for inclusion in the meta-analysis, effect sizes were calculated (along with 95% confidence intervals, CIs) using Cohen's d. When multiple measures of an outcome were used in a study, one effect size was calculated by averaging effect sizes across measures. When only a significance level was reported, the z score corresponding to the p-value was used to estimate the effect size. When outcome data were not reported in a study, and the study authors reported that the groups did not differ, the authors were contacted to obtain exact p-values. When the study authors failed to provide such data, it was assumed that non significance implied no difference between study groups. Calculations were based on intention-to-treat data, where available.

One reviewer abstracted the data on study characteristics and findings using a standardised data extraction form. Two reviewers independently extracted data specific to the effect size calculation. Ambiguous information and disagreements were resolved by discussion amongst multiple reviewers, until a consensus was reached.

**Methods of synthesis**
How were the studies combined?
For studies eligible for inclusion in the meta-analysis, effect size estimates for the outcomes of caregiver burden and active time use were combined using a random-effects model.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. The authors stated that the limited number of trials precluded the use of subgroup analyses.

**Results of the review**
Seventeen trials (n=4,744) were included in the review, of which eight were double-blind placebo-controlled RCTs that met the inclusion criteria for the meta-analysis (n=3,002).

The quality assessment scores for the double-blind placebo-controlled RCTs ranged from 7 (54%) to 12 (92%) out of a possible 13.

**Burden** (4 RCTs, n=1,594).
There was a small, statistically significant reduction in caregiver burden for caregivers of patients with AD who received cholinesterase inhibitors (d=0.18, 95% CI: 0.04, 0.32). There was no significant heterogeneity.

**Time use** (6 RCTs, n=2,286).
There was a small, statistically significant reduction in caregiver time use for caregivers of patients with AD who received cholinesterase inhibitors (d=0.15, 95% CI: 0.07, 0.24). There was no significant heterogeneity.

No results for the other caregiver outcomes were reported.

**Authors' conclusions**
Cholinesterase inhibitors had a small beneficial effect on burden and active time use for caregivers of patients with AD.
**CRD commentary**
The review question was clear in terms of the study designs, participants, interventions and outcomes of interest. The authors specified more strict inclusion criteria for studies to be included in the meta-analysis. Several relevant electronic databases were searched and the search terms were reported. The authors also sought unpublished data, thereby reducing the potential for publication bias. However, only studies reported in English were eligible for inclusion, thus increasing the potential for language bias. The authors stated that the small number of studies identified precluded the use of a funnel plot to investigate publication bias. The study selection procedure was not reported, therefore the potential for reviewer bias and error cannot be assessed. The quality assessment and the majority of the data extraction were undertaken by one reviewer. However, data specific to the effect size calculation were extracted independently by two reviewers, thereby reducing the potential for reviewer bias and error. The criteria used for the quality assessment seem appropriate.

Adequate details of the studies included in the meta-analysis were provided. The results of studies not eligible for the meta-analysis were not reported. Statistical heterogeneity was assessed and the methods used to combine the studies seem appropriate. The authors’ conclusions appear to follow from the evidence presented. This was a reasonably well-conducted systematic review and the conclusions are likely to be reliable.

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

**Research:** The authors stated that future research should investigate whether cognitive, functional or neuropsychiatric benefits to patients with AD mediate benefits to caregivers. They also stated that additional studies may clarify the extent to which cholinesterase inhibitor use affects institutionalisation rates and other long-term outcomes of AD, and that studies pairing patient-directed pharmacotherapy with caregiver-directed interventions (such as stress reduction interventions) would be informative.

The authors also recommended that, in future studies, investigators should specify entry criteria for caregiver participants; they should collect caregiver sociodemographic data; and they should use theoretical frameworks to generate hypotheses, operationally define caregiver-specific variables, select measurement tools and plan data analysis.

**Funding**
National Institute of Mental Health, grant numbers 5 T32 MH19986-08 and P30 MH52247; National Institute of Aging, grant number P50 AG05133.

**Bibliographic details**

**PubMedID**
15935021

**DOI**
10.1111/j.1532-5415.2005.53313.x

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Activities of Daily Living; Alzheimer Disease /drug therapy; Caregivers /statistics & numerical data; Cholinesterase Inhibitors /therapeutic use; Cost of Illness; Humans; Outcome Assessment (Health Care); Socioeconomic Factors; Time Factors
AccessionNumber
12005004066

Date bibliographic record published
31/07/2007

Date abstract record published
31/07/2007

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.