Pharmacological treatment of dementia

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CRD summary
The authors concluded that pharmacotherapy can improve cognitive symptoms and outcomes, there is some evidence for delay in disease progression, and some agents were shown to be effective in patients with vascular dementia. However, few head-to-head studies were found and there were insufficient data relating to efficacy in different subgroups of patients. Despite some minor limitations, the authors’ conclusions are likely to be reliable.

Authors' objectives
To determine the efficacy of pharmacotherapy for dementia syndromes on cognitive symptoms and outcomes.

Searching
The Cochrane CENTRAL Register (February 2003), MEDLINE and PREMEDLINE (1998 to February 2003), EMBASE (1998 to February 2003), AMED (1985 to February 2003), CINAHL (1982 to February 2003), AgeLine (1978 to December 2002) and PsycINFO (1967 to December 2002) were searched for relevant papers published in English; the search terms were reported. The bibliographies of retrieved articles were also checked and experts in the field were contacted.

Study selection
Randomised controlled trials (RCTs) of pharmacological agents (including nutriceuticals) for adults (≥18 years) with a diagnosis of dementia were eligible for inclusion. Accepted diagnostic criteria included the International Classification of Diseases, Diagnostic and Statistical Manual of Mental Disorders, or National Institute of Neurological and Communicative Disorders and Stroke. Crossover trials or trials with a Jadad score of less than 3 were excluded. Studies of populations with alcohol-caused dementia/Korsakoff’s syndrome, Creutzfeldt-Jakob syndrome, spongiform encephalopathy, hypothyroidism, vitamin B12 deficiency, neurosyphilis, all organically caused dementias, temporary dementia, general population of the elderly, or individuals selected for depression were excluded. Studies where dementia was diagnosed using only Lowb, Hachinski criteria (specific for vascular dementia, VaD) were also excluded.

The pharmacological agents included in the review were grouped into three broad categories: cholinergic neurotransmitter modifying agents, non-cholinergic neurotransmitter/neuropeptide modifying agents and ‘other’ agents. The outcomes were categorised into several domains: general cognitive function, specific cognitive function, global assessment, behaviour and mood, quality of life and activities of daily living, caregiver burden, and ‘other’. Further details of the inclusion criteria were given in the report.

Two reviewers independently selected studies for inclusion in the review; any disagreements were resolved by consensus or by discussion with a third reviewer.

Assessment of study quality
The quality of the RCTs was assessed using a modified version of the Jadad scale (maximum score 8 points), and a summary checklist (developed for the review) was used to assess the quality of the reporting of adverse events.

Two reviewers independently performed the quality assessment; any disagreements were resolved by consensus.

Data extraction
In addition to the standard data extracted on patient and trial characteristics, the mean (standard deviation or error), p-value and/or confidence interval (CI) for each time point for each test were extracted in order to calculate weighted mean differences (WMDs) or relative risks (RRs). Both intention to treat and last observation carried forward were used.
Two reviewers independently extracted the data from the primary studies; any disagreements were resolved by consensus or by discussion with a third reviewer.

Methods of synthesis
Studies with the same pharmacological intervention and the same outcome measure were combined in a meta-analysis, using a random-effects model, where three or more studies could be pooled. Consideration was given to the similarity of study populations when selecting studies to be pooled. Summary estimates were reported as WMDs or RRs with their associated CIs. Where pooling was not possible, the studies were combined in a narrative. Summary tables of intervention versus outcome were also presented: these indicated whether a significant effect was observed.

Results of the review
One hundred and eighty-six RCTs (number of participants unclear), evaluating 97 pharmacological agents, were included in the review. There were 72 studies of cholinergic neurotransmitter modifying agents, 61 studies of non-cholinergic neurotransmitter/neuropeptide modifying agents and 76 studies of ‘other’ agents. Twenty-nine studies, evaluating 20 pharmacological interventions, were applied to vascular dementias. The sample sizes ranged from 10 to 978. Overall, few studies were quantitatively combined.

Modified Jadad scores ranged from 5 to 8 for studies of cholinergic neurotransmitter modifying agents, from 5 to 8 for studies of non-cholinergic neurotransmitter/neuropeptide modifying agents, and from 4 to 8 for studies of ‘other’ agents.

Global assessment was improved by donepezil, galantamine, rivastigmine, venacrine, cerebrolysin and idebenone. Cognition (general and specific) was improved by donepezil, galantamine, metrifonate (withdrawn from North America), nicergoline, physostigmine, rivastigmine, velnacrine, cerebrolysin, ginkgo biloba, idebenone and propentofylline. Behaviour and mood was improved by haloperidol. Quality of life and activities of daily living were improved by donepezil, galantamine and posatirelin. Some significant effects of delay of disease progress in mild to moderately severe Alzheimer's disease were found for cerebrolysin, selegiline plus vitamin E, and donepezil. Few head-to-head comparisons (26 studies) found a significant difference between treatment comparisons. However, a superiority for sulphomucopolysaccharides over CDP-choline, donepezil over vitamin E, antagonic-stress over nicergoline and meclofenoxate, posatirelin over citicoline, and pyritinol over hydergine was found. Analyses were stratified by a number of potentially important variables, but the results were inconclusive.

A number of trials in patients with ischaemic VaD demonstrated significant differences in general cognitive function (ateroid, cerebrolysin, donepezil, idebenone and nicergoline) and global assessment (choto-san, donepezil, memantine, nicergoline, propentofylline, vincamine and xantinolnicotinate) with various pharmacological treatments. Seven studies compared VaD populations with other dementia types: 5'-MTHF-trazodone (1 study) and ginkgo biloba (1 study) were found to be effective in patients with multi-infarct dementia, and citalopram was found to effective for patients with VaD (1 study), compared with patients with Alzheimer's disease.

Further results and forest plots were presented in the report, including adverse event data.

Authors’ conclusions
Pharmacotherapy for dementia can improve symptoms and outcomes. Few studies evaluated delay in disease onset or progression, although there is some evidence for delay in disease progression. Few head-to-head studies with other drugs were found, and data relating to the efficacy of pharmacotherapy in different subgroups of patients were limited. Some pharmacological agents were shown to be effective in patients with VaD.

CRD commentary
This broad review question was supported by clearly defined inclusion criteria for the study design and population, while criteria for the intervention and outcomes were more broadly defined. Several relevant databases were searched, but the search was restricted to English language publications and the authors made no attempts to locate unpublished material. As such, it is possible that relevant studies might have been missed and the review may be subject to language and publication bias. The methods used to select papers, assess study quality and extract the data were likely
to have minimised the possibility of reviewer error and bias. The quality of the studies was assessed and only trials meeting a pre-specified quality level on the Jadad scale were included in the review; total scores were provided in an online appendix, although details of the individual components were lacking. Study characteristics were also reported in online appendices. Where appropriate, the studies were combined using standard meta-analytic techniques and statistical heterogeneity was assessed. However, the lack of head-to-head studies limits conclusions. Despite some minor limitations, the authors' conclusions are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that the treating practitioner should set realistic goals for therapeutic intervention.

Research: The authors made several recommendations relating to analytic framework, bias, population, outcomes, analysis and intervention. Recommendations included: longer term studies (>12 months); clearer definitions of efficacy; clarification of the role of industry sponsorship; better conceptualisation and research design to capture critical outcomes (e.g. delay to progression); strategies that account for intention to treat or last observation carried forward; sufficient data to estimate the effect size; better description of the titration process; inclusion of different patient populations; better evaluation of different sub-populations; expansion of outcomes especially carer burden and quality of life; improved collection of adverse events data; and more head-to-head comparisons.

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http://www.ahrq.gov/clinic/epcsums/demphsum.htm

Other publications of related interest

This additional published commentary may also be of interest.


Indexing Status
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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.