Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline


CRD summary
The review concluded that cholinesterase inhibitors and memantine can result in statistically significant but clinically marginal improvement in measures of cognition and global assessment in patients with dementia. This review was generally well conducted and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To determine the effectiveness of cholinesterase inhibitors and the neuropeptide-modifying agent memantine for the treatment of dementia.

Searching
Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, Allied and Complementary Medicine Database, AgeLine and PsycINFO were searched for relevant English language articles from January 1986 through November 2006. References of retrieved papers were also checked.

Study selection
Parallel randomised controlled trials (RCTs) that compared a cholinesterase inhibitor or memantine with placebo or another drug in adults (18 years or older) with major dementia (Alzheimer disease (AD), vascular dementia (VD) and Parkinson dementia (PD)) and mild cognitive impairment were eligible for inclusion in the review. Acceptable diagnostic criteria used to determine dementia included: ICD 9/10; DSM III/III-R/IV (Diagnostic and Statistical Manual of Mental Disorders); NINCDS-ADRDA (National Institute of Neurological and Communication Disorders and Stroke and Alzheimer’s Disease and Related Diseases Association); NINCDS-AIREN (National Institute of Neurological and Communication Disorders and Stroke and Stroke-Association Internationale pour la Recherche et l’Enseignement en Neurosciences). A full list of eligible disease classifications for dementias and severity classification (most studies specifying threshold criteria using the Mini-Mental State Examination (MMSE)) is given in the appendix to the paper. All organically caused dementias, temporary dementia, and studies selected for depression where there was no stratified analysis by disease subgroup (i.e. those with dementia) were excluded. Eligible studies were required to score at least three on the Jadad (original scale).

Primary outcomes were categorised into four main areas: cognition, global function, behaviour, and quality of life (including activities of daily living (ADLs) and caregiver burden). Cognition and global assessment were measured with more than forty different instruments in the included studies, and the most frequently used instruments included: the Alzheimer’s Disease Assessment Scale cognitive subscale (ADAS-cog), the MMSE, the Severe Impairment Battery (SIB), and the clinician-based impression of change (CIBIC), with caregiver input (CIBIC-plus). Other outcomes of interest included rate of institutionalisation, mortality, or adverse events.

Interventions included donepezil (5mg/daily to 10mg/daily), memantine (where reported, final dose was 20mg/daily), tacrine (80mg/daily to 160mg/daily), rivastigmine (1mg/daily to 12mg/daily) and galantamine (final treatment dose ranged from 24mg/daily to 36mg/daily). Comparators included placebo, galantamine and rivastigmine. Most of the included trials were less than one year's duration (range 12 to 52 weeks). The majority of trials were of patients with AD, although some other forms of dementia were also included.

Two reviewers independently selected papers for inclusion in the review.

Assessment of study quality
Study quality was assessed using a modified Jadad scale, which includes additional items concerning collection of adverse event data, description of statistical analysis, and reporting of eligibility criteria. In addition, a checklist for the quality of reporting of adverse events was used which included items on frequency of reporting harms, withdrawals and...
method of collection.

Two reviewers independently assessed the quality of the included studies.

Data extraction
Where data were suitable for pooling, relative risk (RRs) were calculated for binary data (improved, not-improved) and mean differences for continuous data (based on change from baseline scores) with associated 95% confidence intervals (CI). In some cases, estimates of mean change were based on best estimates derived from figures in the citations. Magnitude of change judged to be clinically important was established through a literature search (ADAS-cog >4 points, CIBIC-plus any change, MMSE >3 points).

Specific adverse events were selected a priori and expressed as a percentage for each study (nausea, diarrhoea, dizziness, accidental injury, agitation, urinary disorder, serious adverse events).

Two reviewers independently extracted data from the included studies.

Methods of synthesis
Where appropriate (based on clinical and biological criteria in terms of clinical heterogeneity) studies were combined in a meta-analysis using a random effects model. Summary estimates were reported as weighted mean difference (WMD) or RRs and their 95% CI. Studies were excluded that did not provide a measure of variance for outcomes when computing summary estimates. Where two or more studies provided sufficient information the summary estimates for specific adverse events were calculated. Statistical heterogeneity was assessed using the $\chi^2$ statistic and the $I^2$ statistic. Subgroup analyses by cognitive severity and dementia type were performed.

Results of the review
Fifty-nine RCTs, reporting seventy-five different outcomes, were included in the review.

Donepezil versus placebo (24 RCTs, n=7,556)

A significant change in ADAS cognitive subscale (ADAS-cog) scores was found in favour of donepezil (10mg/daily) in patients with AD (all severity levels) (WMD -2.80, 95% CI: -3.28, -2.33; 5 RCTs) and in patients with donepezil mild/moderate VD (WMD -2.17, 95% CI: 2.99, -1.34; 2 RCTs). No evidence of significant statistical heterogeneity was found. No significant between group difference was found in mild cognitive impairment. Significant statistical heterogeneity was found ($I^2 = 75.5\%$). RRs for improvement from baseline (RR 2.01, 95% CI: 1.58, 2.57; 3 RCTs) and improvement or stabilisation from baseline (RR 1.50, 95% CI: 1.20, 1.89; 1 RCT) in patients with AD (all severity levels, based on the CIBIC-plus) were in favour of donepezil. No evidence of statistical heterogeneity was found. No significant between group difference was found on the CIBIC-plus in patients with mild/moderate VD. Evidence of moderate statistical heterogeneity was found ($I^2 = 55.1\%$). Borderline statistical significance was found in favour of donepezil for ADLs in patients with VD (WMD-0.78, 95% CI: -1.58, 0.01; 2 RCTs). No significant between group difference was found for behaviour (Neuropsychiatric Inventory (NPI)). Donepezil was associated with diarrhoea, nausea, anorexia, dizziness, vomiting in patients with Alzheimer dementia. For vascular dementia, it was associated with abnormal dreams, diarrhoea, nausea, and muscle and leg cramp in patients. In general, the quality of reporting harms was low to moderate.

Donepezil versus galantamine (2 RCTs, n=251) or rivastigmine (1 RCT, n=not reported)

One study found statistical differences in favour of galantamine in a subgroup of patients (MMSE scores between 12 and 18) for changes in cognition (ADAS-cog and MMSE) and scores on the Screen for Caregiver Burden. The second study was pilot study (results not reported). Adverse events most frequently reported were nausea, vomiting, agitation, headache and falls. The rates for all these harms were marginally higher in the galantamine group. No significant difference was found in frequency of serious events.

When donepezil was compared with rivastigmine in patients with moderately severe AD, no significant between group difference was found on measures of cognition and behaviour, but statistically significant changes in global function...
were found in favour of rivastigmine. Subgroup analysis found significant differences on some measures of behaviour and function in patients 75 years or older compared to younger patients. In general, patients receiving rivastigmine reported more adverse events but the frequency of serious events did not differ between groups. The quality of the harms was well reported.

Galantamine versus placebo (10 RCTs, n=3997)

Significant improvement on the ADS-cog score was found in favour of galantamine (24mg/daily) in patients with mild/moderate AD (WMD -2.45, 95% CI:-3.48, -1.42; 6 RCTs) and in patients with AD and VD (WMD -2.70, 95% CI: -3.95, -1.45; 1 RCT). Evidence of significant statistical heterogeneity was found for mild/moderate AD (I² = 75.5%). The RR for improvement or stabilisation from baseline (CIBIC-plus) was statistically significant in patients with mild/moderate AD (RR 1.22, 95% CI: 1.12, 1.33; 4 RCTs) and mild/moderate AD or VD (RR 1.25, 95% CI1.08, 1.45; 1 RCT). No evidence of significant statistical heterogeneity was found. A significant improvement in ADLs were found in favour of galantamine in patients with AD (all severity) (WMD 1.84, 95 % CI: 0.68, 3.00); no evidence of significant statistical heterogeneity was found. Galantamine was associated with anorexia, dizziness, nausea, vomiting and weight loss. Rates of withdrawal due to adverse events ranged from 4 to 17% in the placebo group and 8 to 54% in the galantamine groups. Most studies did not report using a standardised instrument to collect harms data.

Rivastigmine versus placebo (9 RCTs, n= 2164)

Significant statistical improvement on the ADAS-cog was found in favour of rivastigmine (6mg/daily and 12mg/daily) in patients with AD (all severity levels) (WMD -3.91, 95% CI: -5.48, -2.34). However, evidence of significant statistical heterogeneity was found (I² = 90.8%). A significant improvement from baseline on the CIBIC-plus in favour of treatment was found when compared with placebo for patients with AD (all severity levels) (RR 1.76, 95% CI: 1.35, 2.29; 3 RCTs). One study looked at improvement or stabilisation on the same scale in the same patient group but no significant between group difference was found. Statistically significant effect in favour of rivastigmine was found on the Nurses Observation Scale for Geriatric Patients mood subscale (NOSGER-mood) (WMD 3.75, 95% CI: 2.66, 4.85) and the geriatric depression Scale (GDS) (WMD 0.22, 95% CI: 0.15, 0.28); evidence of moderate statistical heterogeneity was found on the NOSGER-mood (I²=36.5%). Rivastigmine was associated with increased abdominal pain, anorexia, dizziness, fatigue, headache, malaise, nausea and vomiting. Rates of withdrawal due to adverse events ranged from 0 to 11% in the placebo groups and 12 to 29% in the rivastigmine groups. Quality of reporting harms varied widely.

Tacrine versus placebo (6 RCTs, n=1203)

One trial found a statistically significant improvement on ADAS-cog for patients receiving tacrine. No significant between group differences were found in the other trials. Elevated alanine aminotransferase levels or other hepatic abnormalities were reported in the treatment group compared to controls in 6 trials. Tacrine was associated with gastrointestinal problems, dizziness, nausea and vomiting. The proportion of patients withdrawing due to adverse events ranged from 0 to 12% in the placebo group compared with 0 to 55% in the tacrine groups. Overall, the quality of procedures used to collect harms data was moderate.

Tacrine versus idebenone (1 RCT, n=not reported)

Results not reported.

Memantine versus placebo (5 RCTs, n=1944)

Significant improvement on the ADAS-cog was found for patients with mild to moderate VD receiving memantine compared with placebo (WMD -2.20, 95% CI: -3.24, -1.15; 2 RCTs). The authors state that a significant difference was found on the CIBIC-plus in patients with Alzheimer dementia and vascular dementia, and that sensitivity analysis did not significantly change the summary effect size, however, only the results of one subgroup are presented (AD (all severity levels), RR 1.25, 95% CI: 1.35, 2.29). No evidence of statistical heterogeneity was found. A significant difference in favour of memantine was found on the NOSGER-mood (VD, all severity levels) and the NPI (AD, all severity levels); no evidence of statistical heterogeneity was found. Adverse events included gastrointestinal symptoms, dizziness, and headaches in patients receiving memantine. However, agitation was found to be more frequently reported...
in the placebo group.

**Authors' conclusions**
Cholinesterase inhibitors and memantine can result in statistically significant but clinically marginal improvement in measures of cognition and global assessment in patients with dementia.

**CRD commentary**
The review question was supported by clear inclusion and exclusion criteria. Several sources were searched for relevant material; although this search was restricted by language and thus some relevant may have been missed. Publication bias was not assessed. Methods used to select studies, extract data and assess study quality were likely to have minimised reviewer error and bias. The quality of the studies was assessed and summary results reported. It may have been better not to have excluded studies at the study selection stage on the basis of quality, but to have included all relevant studies and performed a sensitivity analysis on the basis of this criterion later. Appropriate meta-analytic methods were used, statistical heterogeneity was assessed and sub-group analysis explored. The authors highlight the short duration of many of the studies and that clinically important differences were not consistently evaluated and direct comparisons between agents were limited. Despite some reporting issues, this was a generally well conducted review and the authors’ conclusions are likely to be reliable.

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

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