Review: Cholinesterase inhibitors and memantine consistently but marginally improve symptoms of dementia

Hanna Kaduszkiewicz and Falk Hoffmann

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**QUESTION**

**Question:** How effective are cholinesterase inhibitors and memantine for dementia?

**Outcomes:** Cognitive and global functioning, behaviour, and quality of life measures such as activities of daily living and caregiver burden. Secondary outcomes: mortality, rate of institutionalisation, and adverse events.

**METHODS**

**Design:** Systematic review with meta-analysis

**Data sources:** MEDLINE, Pre-MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, Allied and Complementary Medicine Database, CINAHL and AgeLine were searched from January 1986 to November 2006 for English language articles. Reference lists of identified studies were hand searched.

**Study selection and analysis:** RCTs of cholinesterase inhibitors or memantine in people with major dementia (including Alzheimer’s, vascular and Parkinson’s dementia) compared to placebo or another drug. Measures of cognition were the Alzheimer’s Disease Assessment Scale (ADAS; cognitive and non-cognitive subscales), Severe Impairment Battery (SIB), and Mini-Mental State Examination. The validated measure of global functioning was the clinician-based impression of change with caregiver input (CIBIC-plus). Heterogeneity was investigated using the I² statistic.

**MAIN RESULTS**

Fifty nine RCTs (96 publications) were identified which met inclusion criteria (donepezil vs placebo, 24 RCTs; donepezil vs another drug, 8 RCTs; memantine vs placebo, 5 RCTs; tacrine vs placebo, 6 RCTs; tacrine vs idebenone, 1 RCT; glantamine vs placebo, 10 RCTs; rivastigmine vs placebo, 9 RCTs). See online table for summary estimates of change in cognition vs placebo, galantamine vs placebo, 6 RCTs; rivastigmine vs placebo, 6 RCTs). See online table for summary estimates of effect sizes for the instrument of interest. Concerning the methodological quality of the trials under review, the authors mainly rely on the modified Jadad scale, although using quality scales and checklists is not recommended. They also do not further our knowledge on the question of clinical effectiveness.

In the end, we know what we knew before: (1) The clinical relevance of statistically significant effects of AChI and Memantine on cognition and global function remains an open question. (2) The effects shown hitherto are rather small. (3) A small proportion of patients may respond to drug therapy, but we do not recognise responders in advance. Reflecting the controversy around the clinical evidence, the national regulations concerning prescription and treatment documentation differ strongly between countries. Generally, they tend towards an individualized approach: AChI and Memantine should be prescribed only after an individual consideration of potential benefits and harms, and effects should be monitored regularly and thoroughly.

**CONCLUSIONS**

Cholinesterase inhibitors, with the exception of tacrine, and memantine consistently improve most outcomes in people with dementia, particularly cognition and global functioning, but these improvements are clinically marginal. Meta-analysis is limited by inconsistencies in dementia classifications, the severity of the condition, assessment of outcomes, and reporting of adverse effects.

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