Meta-analysis of six-month memantine trials in Alzheimer's disease

Smith Doody R, Tariot P N, Pfeiffer E, Olin J T, Graham S M

CRD summary
This review compared memantine with placebo in the treatment of probable Alzheimer's disease (AD). The authors concluded that memantine is effective and safe across the spectrum of disease severity. The authors' conclusions reflect the findings of the review for patients with moderate to severe AD and appear reliable. However, benefits were not reported for all outcomes in patients with mild to moderate AD.

Authors' objectives
To assess the efficacy and safety of memantine in Alzheimer's disease (AD), and to determine the effects in differing severities of disease.

Searching
MEDLINE, BIOSIS Previews, International Pharmaceutical Abstracts and the database of Forest Laboratories Inc. were searched in February 2005 for studies published from 1992 to 2004.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) with a treatment duration of approximately 6 months and which met minimum validity criteria (see Validity Assessment) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared memantine with placebo were eligible for inclusion. The included studies used memantine at a dose of 20 mg, given as either one daily dose or two 10-mg daily doses. The duration of most of the included studies was 24 weeks; one study lasted 28 weeks.

Participants included in the review
Studies of patients with a diagnosis of probable AD were eligible for inclusion. Probable AD had to be diagnosed using the criteria of the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) or the American Psychiatric Association's DSM-IV criteria. Patients receiving or not receiving treatment with cholinesterase inhibitors (ChEIs) were eligible for inclusion. Two of the included studies were in patients already taking ChEIs. In the included studies, the mean ages of the patients ranged from 73.8 to 78.2 years and the proportion of females ranged from 52.2 to 71.4%. Three included studies assessed patients with mild to moderate AD who had a Mini-Mental Status Examination (MMSE) score from 10 to 22, while three assessed patients with moderate to severe disease who had an MMSE score of 3 to 14.

Outcomes assessed in the review
Studies that assessed the following outcomes were eligible for inclusion: cognition, clinician's global impression, activities of daily living (function), behaviour and safety (including discontinuation of treatment, several measures of adverse events, and death). The included studies assessed outcomes using a variety of measures, such as: the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-COG), Severe Impairment Battery and the MMSE for cognition; two versions of the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-Plus) for clinician's global impression; two versions of the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) for function; and the Neuropsychiatric Inventory and the Behavioral Rating Scale for Geriatric Patients for behaviour. The review also assessed responders (no change or improvement) and nonresponders (deterioration).

How were decisions on the relevance of primary studies made?
Two reviewers assessed the studies for relevance.
Assessment of study quality
Only double-blind RCTs were eligible for inclusion in the review. Two reviewers assessed this criterion. The studies were also classified as A, B or C according to criteria described by Mulrow et al., and only studies classified as A or B were included.

Data extraction
One reviewer extracted the data and a second reviewer checked the extraction. The mean differences between treatments in the change from baseline were extracted for the primary outcomes on both an intention-to-treat basis, using last observation carried forward, and an observed case basis; the former was regarded as the primary outcome measure. Standardised mean differences (SMDs) for continuous measures and odds ratios for dichotomous outcome measures were calculated. Data were preferentially extracted from published reports rather than from the pharmaceutical company database. Forest Laboratories provided additional data.

Methods of synthesis
How were the studies combined?
The studies were combined in meta-analyses for each outcome measure. Pooled SMDs and pooled odds ratios were calculated with 95% confidence intervals (CIs). A fixed-effect model was reported where no statistically significant heterogeneity was detected, and a random-effects model where significant heterogeneity was found.

How were differences between studies investigated?
Statistical heterogeneity between studies was assessed using the chi-squared and I-squared tests. Subgroup analyses based on disease severity and concomitant use of ChEIs were performed. Sensitivity analyses, in which outliers were removed from the analyses, were also conducted to identify studies responsible for the heterogeneity.

Results of the review
Six RCTs with 2,312 patients were included in the review.

The results for the intention-to-treat analysis are reported below.

Cognition.
There was a statistically significant effect in favour of memantine measured using the ADAS-COG (random-effects model, SMD -0.21, 95% CI: -0.34, -0.08, p<0.001; 6 studies). Significant heterogeneity was found (p<0.04). This effect was also found by the 2 studies which used the MMSE (fixed-effect model, SMD 0.18, 95% CI: 0.03, 0.34, p=0.02). In moderate to severe AD there was a statistically significant effect in favour of memantine (random-effects model, SMD -0.29, 95% CI: -0.54, -0.03, p=0.03). In mild to moderate AD there was a statistically significant effect in favour of memantine (fixed-effect model, SMD -0.15, 95% CI: -0.26, -0.03, p=0.01).

Clinician's global impression.
There was a statistically significant effect in favour of memantine measured using the CIBIC-Plus (SMD -0.19, 95% CI: -0.27, -0.10, p<0.01). In moderate to severe AD there was a statistically significant effect in favour of memantine (SMD 0.27, 95% CI: -0.39, -0.14, p<0.001). In mild to moderate AD there was a statistically significant effect in favour of memantine (SMD -0.12, 95% CI: -0.23, -0.01, p=0.03). Fixed-effect models were used for all of these analyses.

Activities of daily living.
There was a statistically significant effect in favour of memantine measured using the ADCS-ADL (SMD -0.10, 95% CI: -0.18, -0.01, p=0.02). In moderate to severe AD there was a statistically significant effect in favour of memantine (SMD -0.19, 95% CI: -0.32, -0.06, p=0.003). In mild to moderate AD there was no statistically significant difference between the groups (SMD -0.22, 95% CI: -0.13, 0.09, p=0.72). Fixed-effect models were used for all of these analyses.
Behavioural symptoms.

There was no significant difference between the memantine and placebo groups (random-effects model, SMD -0.09, 95% CI: -0.22, 0.04, p=0.05). Significant heterogeneity was found (p=0.05). In moderate to severe AD there was a statistically significant effect in favour of memantine (fixed-effect model, SMD -0.17, 95% CI: -0.30, -0.04, p=0.01). In mild to moderate AD there was no statistically significant difference between the groups (random-effects model, SMD -0.03, 95% CI: -0.21, 0.16, p=0.79).

Subgroup analyses for trials with and without concomitant ChEI treatment were also reported for all outcomes.

There were no significant differences between the memantine and placebo groups on any outcome related to adverse events, including treatment discontinuations, adverse events, serious adverse events and deaths.

Authors' conclusions
Memantine consistently benefited patients in all stages of AD and was well tolerated.

CRD commentary
The review question and the inclusion criteria were clear and specific. The authors searched some relevant electronic databases and although they stated in the 'Methods' section that published studies were sought, three of the 6 included studies were apparently unpublished. It was not clear whether any language restrictions were applied, so the potential for language bias could not be assessed. Thus it was unclear whether all potentially relevant studies were identified. The authors used appropriate measures to minimise the potential for bias and error in the study selection, validity assessment and data extraction processes.

The decision to employ meta-analyses appears appropriate, and sources of variation between the studies were investigated extensively. The review showed that memantine was of benefit in patients with moderate to severe AD, but differences between memantine and placebo were only statistically significant for two of the four outcomes in patients with mild to moderate AD. The authors' conclusions therefore reflect the findings of the review for patients with moderate to severe AD, but only partially reflect the results for patients with mild to moderate AD.

Two of the authors are employees of Forest Laboratories and the other three authors received 'consulting remuneration' for work on the review. Employees of Forest Laboratories reviewed and approved the final version of the review.

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

Bibliographic details

Other publications of related interest

Subject indexing assigned by CRD

**MeSH**
Alzheimer Disease /drug therapy /psychology; Cognition Disorders /drug therapy /etiology; Double-Blind Method; Excitatory Amino Acid Antagonists /therapeutic use; Memantine /therapeutic use; Meta-Analysis; Randomized Controlled Trials as Topic; Treatment Outcome

**AccessionNumber**
12007000854

**Date bibliographic record published**
31/12/2007

**Date abstract record published**
31/12/2007

**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.