Efficacy of memantine on behavioral and psychological symptoms related to dementia: a systematic meta-analysis

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CRD summary
This review assessed efficacy of memantine on dementia-related behavioural and psychological symptoms and concluded that treatment appeared to be beneficial. Although the authors offered an appropriately cautious conclusion based on the limited evidence presented, the reliability of the review is potentially compromised by bias and error in the search and selection of studies.

Authors' objectives
To assess the efficacy of memantine as a therapeutic agent for the treatment of behavioural and psychological symptoms related to dementia.

Searching
MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL) and Pharm-line, ClinicalTrials.gov and Current Controlled Trials were searched from 1966 to July 2007 for English language articles. Search terms were reported. Reference lists of retrieved papers and conference proceedings were reviewed. Manufacturers contacted for additional studies.

Study selection
Placebo-controlled, double-blind randomised controlled trials (RCTs) of patients with behavioural and psychological symptoms related to dementia (rated with the Neuropsychiatric Inventory, NPI) who had probable Alzheimer's Disease (consistent with National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria) were eligible for inclusion. Treatment (memantine or matched placebo) had to be administered for at least one month. Crossover and open-label trials were excluded.

In included trials, the mean age of the participants ranged from 73.8 to 78.2 years; the proportion of males ranged from 21.8 to 48.2%. The duration of the included trials ranged from 24 weeks to 28 weeks. The included trials were heterogeneous, particularly in terms of disease severity and use of concomitant cholinesterase inhibitor therapy (cholinesterase inhibitor combinations were included and compared, although this did not match the inclusion criteria for the review). All trials used memantine doses of 20mg daily.

Two reviewers independently applied the inclusion criteria and selected the studies.

Assessment of study quality
The quality of the included trials was assessed using the Jadad scale. Randomisation, allocation concealment, blinded outcome assessment and withdrawal/drop-out were assessed; the score for each trial was reported (traditionally ranging from 0 to 5, with 5 being the maximum achievable score).

Two reviewers assessed quality and resolved discrepancies by consensus. A third reviewer was consulted for unresolved disagreements.

Data extraction
The change in mean NPI scores from baseline to endpoint in treatment and placebo groups was extracted to calculate mean difference (MD), with standard errors (SEs). Standard errors were extracted from figures, or they were estimated from the pooled weighted averages of standard deviations (SDs) if standard errors were not available. Standard deviations were calculated from standard errors if standard deviations were not reported. Cohen effect sizes were calculated from the difference between the treatment and placebo means divided by their standard deviations. The last observation carried forward approach was used in all the trials included in the analysis to impute missing data. The number of participants lost to follow-up in each arm was extracted and reported.
It appeared that more than one reviewer extracted the data.

**Methods of synthesis**
The effect of memantine was assessed in a meta-analysis by pooling mean differences using the inverse squared standard errors component of the fixed-effect model. However, if Cohen’s test for trial homogeneity demonstrated a significant heterogeneity, a random-effects model was used.

Heterogeneity between trials was assessed by $I^2$ statistic and meta-regression analyses.

**Results of the review**
Six RCTs met the inclusion criteria, but the five trials (n=1,750 participants) that provided Neuropsychiatric Inventory (NPI) scores between the pre- and post-intervention periods were included in the analysis. Three trials achieved a Jadad score of 5 points and three trials had a score of 2. Losses to follow-up after the first measurement in the trials ranged from 11 to 27%. Two of the trials were parallel group, double-blind randomised controlled trials, and four were placebo controlled trials.

Memantine demonstrated a statistically significant improvement in NPI scores compared with placebo (MD -1.99, 95% CI -0.08 to -3.91; five trials, n=1,750 participants; $I^2$=55.93%).

**Authors' conclusions**
Initial data appeared to indicate that memantine decreased NPI scores and may have a role in managing behavioural and psychological symptoms related to dementia. However, limitations with the current data mean that it was unclear whether the benefit demonstrated with memantine was clinically significant.

**CRD commentary**
This review addressed a well-defined question in terms of participants, interventions, outcomes, and study design. However, there appeared to be a discrepancy between the inclusion criteria and what was actually included; this may have potentially affected the reproducibility and reliability of the review. The search included appropriate databases, but was restricted to English, so the potential for language bias could not be ruled out. Two reviewers independently selected the studies and assessed quality of the included studies using standard criteria. It appeared that the similar efforts to minimise error and bias were applied to data extraction. Potential sources of heterogeneity were explored; the methods used were appropriate.

Although the authors offered an appropriately cautious conclusion based on the limited evidence presented, the reliability of the review is potentially compromised by bias and error in the search and selection of studies.

Four of the authors disclosed financial links with Lundbeck Pharmaceuticals and/or Forest Laboratories (both manufacturers of memantine).

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

**Research:** The authors stated that further trials focusing on the most clinically relevant subgroup of behavioural and psychological symptoms related to dementia are needed including patients with significant scores on standard scales and assessing effect of memantine in prevention of further crises. Also, further research is needed to investigate the mode of action for any psychotropic effects of memantine.

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Not stated.

**Bibliographic details**
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.