Efficacy and safety of antidepressants for treatment of depression in Alzheimer's disease: a metaanalysis

Thompson S, Herrmann N, Rapoport M J, Lanctot K L

CRD summary
The review assessed the efficacy and safety of antidepressant therapy for depression in patients with Alzheimer's disease. The authors' conclusion that antidepressant therapy was effective, with rates of discontinuation comparable to placebo, followed from the results presented, but may be overstated given the small number of included studies and the small data set.

Authors' objectives
To assess the efficacy and safety of antidepressant treatment for depression in patients with Alzheimer's disease.

Searching
MEDLINE (January 1966 to June 2006) and the Cochrane Database of Controlled Trials were searched; search terms were reported. References from retrieved articles were checked. Only English-language publications were included.

Study selection
Randomised double-blind placebo controlled trials of adults with a diagnosis of Alzheimer's disease and depression treated with antidepressants were eligible for inclusion. Interventions included imipramine, clomipramine, sertraline and fluoxetine. Most of the included participants were out-patients, but one study included women from a nursing home. Duration of study lasted between six and 12 weeks. The main outcomes of interest were response to treatment, remission of depressive symptoms, change in cognition as measured by the Mini-Mental State Examination (MMSE) and treatment discontinuation (for any reason and due to an adverse event). Response to treatment was defined as a ≥50 per cent reduction in a standardised measures for depression. Remission was defined as a score <8 on the 17-item Hamilton Depression Rating Scale. Other definitions were considered if they were deemed to be clinically valid.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Two reviewers assessed the quality of the included studies using the Jadad Scale. Each study was given a total score from a maximum of 5.

Data extraction
Odds ratios were calculated for binary outcomes and weighted mean differences were calculated for continuous outcomes, along with associated 95% confidence intervals (CI). In addition, the number needed to treat (NNT) and number needed to harm (NNH) were calculated. Two reviewers extracted data from the included studies. Any discrepancies were resolved through consensus.

Methods of synthesis
Studies were pooled for each outcome in a meta-analysis using a random-effects model. Statistical heterogeneity was assessed using the \( \chi^2 \) test and the \( I^2 \) statistic. Publication bias was evaluated through the visual examination of funnel plots where there were five or more studies.

Results of the review
Five randomised controlled trials (RCTs) were included in the review (n=165): four parallel RCTs and one cross-over RCT. All studies had a Jadad score of 3 or more.

Antidepressant efficacy (three RCTs, n=116): A statistically significant effect in the proportion of patients who experienced a reduction in depressive symptoms (odds ratio was 2.32, 95% CI: 1.04 to 5.16) and the proportion of
patients who experienced remission of depressive symptoms (odds ratio was 2.75, 95% CI: 1.13 to 6.65) was found in favour of antidepressant therapy compared to placebo; number needed to treat was five for both reduction in depressive symptoms (95% CI: 3 to 59) and remission of depressive symptoms (95% CI: 2 to 24). No evidence of significant statistical heterogeneity was found.

Cognitive change (three RCTs, n=113): No statistically significant between-group difference was found for change in cognition as measured by the Mini-Mental State Examination. No evidence of significant statistical heterogeneity was found.

Safety: No statistically significant between-group differences were found for overall drop out rates (five RCTs, n=165) or drop-out rates due to adverse events (four RCTs, n=137). No evidence of significant statistical heterogeneity was found.

No evidence of publication bias was found.

Authors’ conclusions
Antidepressant treatment for depression in patients with Alzheimer's disease was effective. Rates of discontinuation were comparable to placebo. However, clinicians should be vigilant for potential harmful effects of this treatment in this population.

CRD commentary
The review was supported with clear inclusion and exclusion criteria. Two databases were searched, however, the search was limited to papers published in English and no attempts were made to locate unpublished material, which raised the possibility of language and publication bias. Although publication bias was assessed, the small number of studies limited the reliability of this assessment. Methods used to extract data and assess validity were likely to minimise the likelihood of reviewer error and bias, however, it was unclear whether similar methods were used to select studies for inclusion in the review. A standardised scale was used to assess the validity of the included studies, although only a summary score was reported. Standard meta-analytic techniques were used to pool the studies and statistical heterogeneity was assessed. The authors highlighted a number of methodological limitations, including small sample size, low dosages and short duration of treatment. The conclusions followed from the results presented, but are perhaps overstated given the limited number of studies included and the small data sets used.

Implications of the review for practice and research
Practice: The authors stated that antidepressant prescription in dementia patients should be started slowly at a low dosage. Clinicians should be vigilant for evidence of adverse events, which may be identified by behavioural changes, as patients may not be able to verbally communicate such effects.

Research: The authors stated that more large-scale RCTs were needed to assess the effectiveness and safety of antidepressants for patients with Alzheimer's disease. Future studies should use standardised depression measures in Alzheimer's disease diagnostic criteria.

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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.