A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia

Nelson JC, Devanand DP

CRD summary
The review found that evidence for the effectiveness of antidepressants in people with dementia and depression was inconclusive and that larger studies were required. The review was generally well conducted and these findings appear reliable.

Authors' objectives
To evaluate the efficacy of antidepressants for people with depression and dementia.

Searching
MEDLINE (from 1966) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to May 2010. Search terms were reported. The reference lists of articles retrieved were checked for further studies.

Study selection
Eligible were double-blinded placebo-controlled parallel-group randomised controlled trials (RCTs) of antidepressants marketed in the USA. Participants were required to have acute-phase depression and dementia diagnosed by established criteria. Required outcomes were response, remission, symptom change (using objective measures) and treatment discontinuation. Detailed definitions of outcomes were provided in the review.

The included studies were conducted in outpatient, in-patient and residential settings. Participant age ranged from 70 to 89 years, most participants were female (47% to 100%). Most studies were restricted to participants with Alzheimer’s disease and most required participants to have a Mini-Mental State Examination score of 10 to 27. Baseline severity of depression varied widely. No studies differentiated between participants with and without a previous history of early onset recurrent depression. Studies used various antidepressants including tricyclics, antidepressants, serotonin reuptake inhibitors and venlafaxine; in most cases with an ascending dose schedule. Various scale-based criteria and global ratings were used to assess response and remission rates; three different (named) symptom scales were used. Trial duration ranged from six to 12 weeks.

Two reviewers selected and agreed which studies to include.

Assessment of study quality
Study quality was evaluated with the Jadad scale reported randomisation, double blinding and management of drop-outs. Studies were awarded a score out of 5 points.

The authors did not state how many reviewers performed the assessment.

Data extraction
For dichotomous outcomes, odds ratios (ORs) and 95% confidence intervals (CIs) were extracted or calculated. The last observation carried forward in the intention-to-treat sample was used, unless only data from completers were available. Standardised mean differences from baseline and their standard deviation were calculated for continuous outcomes. If the standard deviation of the change score was unavailable, the standard deviation of the end score was used. Authors of primary studies were contacted for more information where required.

One reviewer extracted data, which were checked by a second reviewer.

Methods of synthesis
The studies were combined to calculate pooled odds ratios and standardised mean differences with 95% CIs, using a Mantel-Haenszel random-effects model. Heterogeneity was assessed using $X^2$ and $I^2$. Sensitivity analyses were conducted to examine the effects on response and/or remission rate of depression diagnosis and severity, trial duration
and exclusion of RCTs with the highest and lowest odds ratio. Publication bias was assessed with a funnel plot.

**Results of the review**

Seven RCTs were included in the review (336 participants, range 24 to 131). Trial quality ranged from good to excellent; Jadad scores were 5 (two RCTs), 4 (four RCTs) and 3 (one RCT). All RCTs described diagnostic criteria and used an objective depression scale and the Mini-Mental State Examination. Five used intention-to-treat analysis and three defined the primary outcome. None described their method of randomisation.

One of three RCTs that defined a primary outcome found significant evidence of efficacy. One of the four other RCTs found a significant benefit from antidepressants. When studies were pooled, the intervention had no significant effect on rates of response (six RCTs), remission (five RCTs), change scores (six RCTs) or rates of treatment discontinuation (either overall or due to adverse events; both seven RCTs). Heterogeneity was significant for response rate ($I^2=56\%$), moderate for remission rate ($I^2=49\%$) and low or absent for other outcomes.

No evidence of publication bias was found. The results of sensitivity analyses were also reported.

**Authors' conclusions**

Evidence for the effectiveness of antidepressants in people with dementia and depression was inconclusive and larger studies were required.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies. Only two databases were searched and it was not stated whether the search was limited by language or publication status. No evidence was found of publication bias though there may have been too few studies to detect this. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer involved in selection of studies and data extraction. It was unclear whether similar precautions applied to validity assessment.

Appropriate statistical techniques were used to combine the studies and to assess and explore heterogeneity. As the authors noted, the studies were few and were too small to detect meaningful effects from the interventions. Clinical and methodological variations made it difficult to interpret the findings.

The review was generally well conducted and the authors’ findings appear reliable.

**Implications of the review for practice and research**

**Practice:** Authors stated that clinicians should consider evidence from older and mixed-aged populations without dementia when treating depression with dementia. They recommended using antidepressants in this population for treating major depression if severe, recurrent and/or in those with a history of drug response, while allowing for potential longer-term side-effects (such as falls and fractures). They also stated that patients and families should be told that antidepressant efficacy was not established in this situation, and that supportive elements of clinical management may be beneficial.

**Research:** Authors stated that future studies should target those with dementia most likely to respond to antidepressants, such as those with moderate to severe unipolar non-psychotic major depression. Studies should distinguish between those with a history of early onset recurrent depression and those for whom the first episode was associated with dementia. They advised that 796 participants would be needed to achieve 80% power to detect differences.

**Funding**

No external funding.

**Bibliographic details**


**PubMedID**

21453380
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.