Efficacy of second generation antidepressants in late-life depression: a meta-analysis of the evidence

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CRD summary
The authors concluded that antidepressants seem effective for late-life depression but effects are modest and variable; adverse effects are significantly more likely with antidepressants than with placebo. The review was well-conducted and these conclusions appear reliable, with the proviso that the number of trials was small and that the results may not be generalisable to the frail elderly.

Authors' objectives
To assess the efficacy of second generation antidepressants for late-life major depression.

Searching
The Cochrane Central Register of Controlled Trials (2006, Issue 3) and MEDLINE (1966 to August 2006) were searched. Search terms were reported. Previous reviews and the proceedings of psychiatric meetings since 2000 were hand searched. Pharmaceutical manufacturers were contacted seeking further studies. Both published and unpublished trials were sought.

Study selection
Double-blinded parallel-group randomised placebo controlled trials of acute phase oral second-generation (non-tricyclic) antidepressants marketed in the USA were eligible for inclusion. Participants were required to be community dwelling adults at least 60 years old, with non-psychotic unipolar major depression not associated with a medical disorder (such as stroke or dementia).

Outcomes of interest were response, remission and change scores on the Hamilton Depression Rating Scale (HAMD) or the Montgomery Asberg Depression Rating Scale (MADRS). Response was defined as an improvement from baseline of 50% or more on either scale. Remission was defined as in the primary study.

The mean age of participants in the included studies was 68 to 80 years and the proportion of women ranged from 46% to 76%. In most cases the mean severity of depression was moderate. All studies excluded participants with evidence of cognitive impairment indicated by a high Mini-Mental State Examination score, but the cut-off score varied from 18 to 25. The antidepressants utilised were bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine. All studies used the HAMD or MADRS scales to measure outcomes. The studies were of 6 to 12 weeks’ duration, and all were sponsored by antidepressant manufacturers.

Study selection was conducted by two reviewers who agreed upon which studies met the inclusion criteria.

Assessment of study quality
Study quality was evaluated using the Jadad scale, which measures adequacy of randomisation, blinding, and management of withdrawals and drop-outs.

The authors did not clearly describe how the assessment was performed.

Data extraction
For binary outcomes, odds ratios (ORs) and absolute risk differences (RDs) with 95% confidence intervals (CIs) were calculated from the number of events occurring in the two groups. For continuous outcomes mean differences between the change score in the two groups were calculated, with 95% CIs. If the standard deviation (SD) of change scores was not reported or not calculable, it was imputed using the largest SD reported in other studies. Where studies reported two different formulations of antidepressant they were combined; where two different doses were utilised they were not combined. An intention to treat approach was used, using the last observation carried forward in participants with one or more outcome measure. Where studies did not report complete information, it was obtained through other data.
presentations or by contact with trial personnel.

Data were extracted by one reviewer and checked by a second, with discrepancies resolved by consensus.

**Methods of synthesis**

Data were combined using a Peto fixed-effect model to calculate pooled ORs, RDs, and 95% CIs for each outcome, weighted for study sample size and event rate. In addition, pooled event rates for each group were expressed as a percentage, and numbers needed to treat (NNT) were reported for the primary outcomes. For continuous data, mean differences were combined to obtain weighted mean differences (WMDs), 95% CIs and p values, using an inverse variance fixed effect model weighted for sample size. Heterogeneity was assessed using the $I^2$ test and $I^2$ statistic, with $p<0.20$ and 50% (respectively) taken to indicate heterogeneity. Where heterogeneity was detected, the effect on the $I^2$ statistic of excluding individual studies was investigated. The effect of a random-effects model was also tested.

Publication bias was assessed using a funnel plot.

Subgroup analyses were conducted to assess whether effects differed between selective serotonin reuptake inhibitors (SSRIs) and other drugs and whether study duration affected outcomes. Differences between subgroups were investigated with the $\chi^2$ test.

**Results of the review**

Ten randomised controlled trials (RCTs) with 13 comparisons were included (n=4237, sample size ranged from 174 to 747). The Jadad score of the included studies was 4 or 5 (out of 5), denoting good to excellent quality. Drop-out rates across study groups ranged from 11 to 36%.

Response and remission (10 RCTs, 13 comparisons) Response and remission rates were significantly higher in the intervention group; response rates OR 1.40 (95% CI: 1.24, 1.57, p<0.001, NNT 13); remission rates OR 1.27 (95% CI: 1.12, 1.44, p<0.001, NNT 20). Pooled response rates were 44.4% and 32.6% for antidepressants, 34.7% and 26.5% for placebo, respectively.

Depression scores (8 RCTs, 10 comparisons) Changes in the HAMD were significantly greater in the intervention group (WMD 1.40, 95% CI: 0.89, 1.90, p<0.003).

Discontinuation (10 RCTs, 13 comparisons) Discontinuation rates due to any reason/adverse effects were significantly higher in the intervention group (OR 1.22, 95% CI: 1.06, 1.40, p<0.005; OR 1.84, 95% CI: 1.51, 2.24, p<0.001; respectively). Pooled discontinuation rates were 24% and 12% for antidepressants; 20% and 7% for placebo, respectively.

Heterogeneity There was significant heterogeneity in rates of response (p=0.003, $I^2$=64.6%) and remission (p=0.001, $I^2$=67.5%), depression scores (p=0.02, $I^2$=53.3%) and discontinuations due to adverse effects (p=0.002, $I^2$=61.1%). A single RCT was responsible for about half the variability due to heterogeneity. This RCT had the highest placebo response rate and involved many centres. The funnel plot showed no evidence of publication bias.

Subgroup analyses The effects of SSRIs appeared similar to those of other antidepressants (8 RCTs, 10 comparisons). Response rates were significantly higher in the 10 to 12 week studies than the 6 to 8 week studies (p<0.01).

**Authors' conclusions**

Antidepressants seem effective for late-life depression but effects are modest and variable. Adverse effects are significantly more likely with antidepressants than with placebo.

**CRD commentary**

The objectives and inclusion criteria of the review were clear, relevant sources were searched for published and unpublished studies and suitable criteria were used to assess validity. Steps were taken to minimise the risk of bias and error, by having more than one reviewer independently involved in study selection and data extraction, though it is unclear whether this also applied to validity assessment. Appropriate statistical methods were used to combine studies and to check for heterogeneity and publication bias. Potential sources of heterogeneity were appropriately investigated by subgroup analyses and by discussion in the text, which highlighted the marked clinical and methodological differences between the studies. However, it should be noted that there were discrepancies between the numbers cited.
in the text and those given in the included RCTs table for the numbers of patients analysed. Otherwise, the review was well-conducted and the authors’ conclusions appear reliable, with the proviso that the number of trials was small and that the results may not be generalisable to the frail elderly.

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

Practice: The authors stated that decisions on use of antidepressants for late-life depression must weigh the likely benefits (which are modest and variable during acute treatment) against potential safety issues. Effectiveness appears to increase over time.

Research: The authors stated that patient-level analyses may help identify the characteristics of responders and non-responders to antidepressants for late-life depression.

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