Meta-analysis of trials comparing antidepressants with active placebos

Moncrieff J, Wessely S, Hardy R

Authors' objectives
To investigate the efficacy of antidepressants versus active placebo.

Searching
MEDLINE, EMBASE and PsycLIT were searched using the keywords 'active placebos' and 'atropine'. Trials identified from handsearches of major psychiatric journals, and reference lists of published reviews, were examined for additional material.

Study selection
Study designs of evaluations included in the review
The included studies were double-blind, random allocation trials that used an active placebo, treated depression, used an antidepressant currently regarded as efficacious, and made some outcome assessment of mood.

Specific interventions included in the review
Antidepressants versus active placebo.

The antidepressants were imipramine (133 to 220 mg), amitriptyline (100 to 157 mg), amitriptyline-perphenazine combination, and nortriptyline (100 to 150 mg).

The active placebos were atropine (0.4 to 1.25 mg), and atropine (0.1 to 0.15 mg) with phenobarbital sodium (10 to 15 mg)).

Participants included in the review
Depressed patients aged from 19 to 75 years, who were being treated on an in- and out-patient basis. The proportion of females in the studies ranged from 60 to 100%.

Outcomes assessed in the review
The change in mood at the end of treatment was defined as the outcome of interest. This was measured by various rating scales: the 'response to treatment' category scores; Total Distress Score; 3, 4, or 5 categories of improvement scores; the Hamilton Rating Scale for Depression; the In-Patient Multidimensional Psychiatric Scale; or the Global Clinical Improvement Scale.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed quality.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

For each trial, changes in the various mood scores were converted into effect sizes, using intention to treat data where possible.
Methods of synthesis
How were the studies combined?
The overall effect size was calculated using a fixed-effect model, weighting each individual effect size by the inverse variance.

How were differences between studies investigated?
All pooled calculations included a test for heterogeneity. A subgroup analysis of in- and out-patients, defined a priori, was also performed. Sensitivity analyses were conducted using various combinations of trials and estimates.

Results of the review
Nine trials were included: 8 parallel groups and 1 crossover study. There were 815 participants, of which 752 completed the studies (395 in the treatment groups and 357 in the active placebo group).

Only 2 of the 9 studies produced effect sizes which showed a consistent significant difference in favour of the active drug.

Combining all studies, using a fixed-effect model, produced a pooled effect size of between 0.41 (95% confidence interval, CI: 0.27, 0.56, p<0.001) and 0.46 (95% CI: 0.31, 0.60, p<0.001) with high heterogeneity due to one strongly positive trial: heterogeneity ranged from 38.0 (p<0.001) to 37.3 (p<0.001).

Sensitivity analyses, excluding 2 trials, reduced the pooled effect size to between 0.21 (95% CI: 0.03, 0.38, p=0.02) and 0.27 (95% CI: 0.10, 0.45, p=0.002).

Authors’ conclusions
The more conservative estimates produced in this review suggest that unblinding effects may inflate the efficacy of antidepressants in trials using inert placebos.

CRD commentary
The authors stated the review question, inclusion criteria, study details, and the methodology for pooling in a comparison of the available literature.

The authors searched the literature but did not reported search dates, language restrictions, or whether unpublished data were sought. This strategy may have missed relevant material, making duplication of the search difficult.

The authors reported the inclusion criteria and study design, but did not describe how the decisions to include studies were made, or on what basis the included studies were judged to be relevant. There was also no quality review of the included studies.

The conclusions in this review should be viewed with caution since the included trials were not recent (1961 to 1984), were not reviewed for quality, and were based on trials with a very small number of participants.

A related commentary on this article argues a bias on the part of the review’s authors (see Other Publications of Related Interest).

Implications of the review for practice and research
Practice: There are no stated implications for practice.

Research: The authors state that active placebos are necessary to provide comparable conditions for control groups in further research on existing antidepressants. However, trials of new antidepressants should include both inert and active placebos to obtain reliable evidence of their effect.
Funding
South Thames NHS Executive.

Bibliographic details

PubMedID
9614471

Other publications of related interest
This additional published commentary may also be of interest. Healy D. Commentary: meta-analysis of trials comparing antidepressants with active placebos. Br J Psychiatry 1998;173:232-4.

Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Adult; Aged; Antidepressive Agents /therapeutic use; Bias (Epidemiology); Clinical Trials as Topic /standards; Depressive Disorder /drug therapy; Double-Blind Method; Female; Humans; Male; Middle Aged; Placebos; Sensitivity and Specificity

AccessionNumber
11998000559

Date bibliographic record published
30/09/1999

Date abstract record published
30/09/1999

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.