Antidepressants for the treatment of depression in neurological disorders: a systematic review and meta-analysis of randomised controlled trials

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CRD summary
The authors concluded that antidepressants were more effective than placebo for treatment of depression in adults with neurological disorders. It remained uncertain whether antidepressants significantly improved quality of life, function and cognitive outcomes. Uncertainty around trial quality, lack of reporting or exploration of variability between trials, and unexplained inconsistency of data mean that the reliability of the authors' conclusions is unclear.

Authors' objectives
To compare the effectiveness of antidepressants versus placebo for treatment of depression in adults with neurological disorders. To determine the effectiveness of antidepressants for improving quality of life, and functional and cognitive outcomes.

Searching
Databases held by the Cochrane Collaboration Depression, Anxiety and Neurosis Review group (CCDAN), MEDLINE, EMBASE, and PsycINFO were searched up to August 2009 (start date not reported); search terms were reported. Reference lists from included studies and related reviews were scanned. National, international and pharmaceutical industry trial registers were searched to identify unpublished data.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared depression scores following antidepressant versus placebo treatment of depressive disorders in adults with co-morbid neurological disorders. Symptom-based neurological conditions, dementia and mild cognitive impairment were excluded. Depression score ratings were the primary outcome, assessed with validated tools at four to five weeks, six to eight weeks, nine to 18 weeks and over 18 weeks following randomisation.

The included trials investigated antidepressants for post-stroke depression, Parkinson's disease, multiple sclerosis, brain injury, and epilepsy. Antidepressants were mainly specific serotonin re-uptake inhibitors and tricyclics, in daily doses that ranged from 4mg to 300mg.

Two reviewers selected studies for inclusion independently. Discrepancies were resolved by consensus between two additional reviewers.

Assessment of study quality
The Cochrane Collaboration's domain-based tool was used to assess allocation concealment, sequence generation, blinding, selective outcome reporting, and drop-outs. The Van Tulder quality assessment scale for RCTs was used to quantify risk of bias (score ranged from 0 to 11); a score of 6 or more indicated low risk.

The authors did not report how many reviewers performed the quality assessment.

Data extraction
Dichotomous data (recovery versus remission) and continuous data (mean depression score and standard deviation) were extracted at the four time points pre-specified in the eligibility criteria. Secondary outcomes extracted were number of adverse events and drop-outs, and scores from validated tools measuring quality of life, and functional and cognitive outcomes at six to eight weeks, nine to 18 weeks, and over 18 weeks post randomisation. Missing data were obtained by direct contact with the authors. Two imputation methods were used to impute primary outcome data when possible.

Two reviewers extracted the data independently. Discrepancies were discussed and resolved by a third reviewer when necessary.
Methods of synthesis
Odds ratios, with 95% confidence intervals, were calculated from dichotomous data of individual trials and pooled using the Mantel-Haenszel method. Standardised mean differences, with 95% confidence intervals, were calculated from continuous data for continuous data of individual trials (statistical pooling method not reported). Random-effects models were used for meta-analyses (where reported). Two trials were excluded from the primary meta-analysis due to insufficient depression score data. Heterogeneity was assessed using $I^2$, with scores of 50% or more indicating significant heterogeneity. Sensitivity analyses for treatment efficacy at six to eight weeks were conducted by removing outliers.

Secondary outcomes were reported in a narrative synthesis.

Results of the review
Twenty RCTs were included in the review, with 18 RCTs included in the meta-analysis (n=1137 participants, range 12 to 229). Length of follow-up ranged from four weeks to 78 weeks. The median Van Tulder quality assessment scale score was 5 (range 1 to 10).

Among ten trials reporting recovery versus remission at six to eight weeks, antidepressant treatment was associated with greater than twofold odds of remission compared with placebo treatment (OR 2.23, 95% CI 1.54 to 3.23; n=683; $I^2=0\%$). Weaker significance for this association was found with mean depression scores and standard deviations, reported by eight trials at the same time point (SMD -0.61, 95% CI -1.13 to -0.10; n=566); substantial heterogeneity was demonstrated ($I^2=86\%$).

The combined positive effect of antidepressants at six to eight weeks remained statistically significant in all sensitivity analyses, except for the analysis of mean depression ratings (continuous data) of trials that used a narrow definition of depression (SMD -0.39, 95% CI -1.18 to 0.40; two trials).

Narrative synthesis of the secondary outcome results (quality of life, functional and cognitive measures) was reported in the review.

Authors’ conclusions
Compared with placebo treatment, antidepressants were effective for treatment of depression in adults with neurological disorders. There was insufficient evidence to determine the efficacy of antidepressants in improving quality of life, and functional and cognitive outcomes.

CRD commentary
The review question and inclusion criteria were clear. The search was updated twice and grey literature was identified via searches of reference lists and trial registers. Publication bias seems unlikely, although no formal tests were performed. Language restrictions were not reported, so the presence of bias remained unclear. Screening and data extraction were performed by more than one reviewer, which reduced the risk of reviewer error and bias, although the number of reviewers that performed the quality assessment was not reported.

The included trials were assessed for methodological quality using a validated tool that produced a summary score, and for risk of bias using the Cochrane domain-based tool. The inclusion of trials judged to be of poor quality (summary score result) was explored by sensitivity analyses, but the use of summary scores may be misleading. Pooled odds ratios and standardised mean differences reported by meta-analysis of dichotomous and continuous data were appropriate, although standardised mean differences were poorly reported. Heterogeneity ($I^2$ values) was reported for primary outcome data at all time points, but substantial heterogeneity was not explored. The impact of missing data was explored in sensitivity analyses, but the amount of data imputed was not reported; the extent to which it influenced the findings was unclear. Depression severity was significantly improved for antidepressant treatment over placebo treatment and was stated in the authors’ conclusions, but the variation in results across time points was not discussed, so their conclusion on efficacy of antidepressants appeared overly positive.

One reviewer acted as an expert witness in a litigation relating to paroxetine.

The review processes appear to have been well conducted, but the small number of poor quality trials used for the primary outcome meta-analyses, unexplored variation in results across time points, and unexplained heterogeneity
suggest that the reliability of the authors’ conclusions is unclear.

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

**Practice:** The authors stated that this review showed that antidepressant treatment for adults with neurological disorders could be recommended, but that it was uncertain whether this applied to all neurological disorders.

**Research:** The authors stated that further RCTS investigating antidepressant efficacy and safety for this population were required.

**Funding**

European Palliative Care Research Collaborative funding from the European Commission’s Sixth Framework Programme.

**Bibliographic details**


**PubMedID**

21558287

**DOI**

10.1136/jnnp.2010.230862

**Original Paper URL**

http://jnnp.bmj.com/content/82/8/914.abstract

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Adult; Antidepressive Agents /therapeutic use; Cognition /drug effects; Depression /drug therapy; Humans; Nervous System Diseases /psychology; Quality of Life; Randomized Controlled Trials as Topic; Treatment Outcome

**AccessionNumber**

12011005287

**Date bibliographic record published**

02/11/2011

**Date abstract record published**

28/02/2012

**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.