Antidepressants for the treatment of depression in palliative care: systematic review and meta-analysis


CRD summary
The review found that antidepressants were effective in treating depression in palliative care but it was possible that efficacy may have been overestimated due to selective reporting and publication biases. The reliability of these conclusions was unclear as the appropriateness of pooling across drug classes was questionable.

Authors’ objectives
To assess the efficacy of antidepressants for the treatment of depression in palliative care.

Searching
MEDLINE, EMBASE and PsycINFO were searched to December 2009 and search terms were reported (no language limitations reported). The Cochrane Depression, Anxiety and Neurosis Group searched their trials register and national, international and pharmaceutical trials registers were examined. Reference lists of included studies and relevant reviews were scanned for further studies.

Study selection
Randomised controlled trials (RCTs) that compared any type of antidepressant with placebo in adults over 18 years old with depression in the context of a life-threatening illness were eligible for inclusion. Eligible trials had to report depression as the primary outcome (defined as ≥50% improvement, or depression score). Secondary outcomes assessed were acceptability (in terms of drop-outs), tolerability (number of adverse events), quality of life and functional status.

The included participants had cancer, renal failure, chronic obstructive pulmonary disease, chronic heart failure, Parkinson's disease, multiple sclerosis or HIV/AIDS. Depression was diagnosed with a variety of measures. A variety of antidepressants were used, mainly tricyclic antidepressants and selective serotonin reuptake inhibitors; doses ranged from 10 to 300mg.

Two reviewers independently assessed studies for inclusion; disagreements were resolved by discussion and consultation with two further reviewers.

Assessment of study quality
Methodological quality was assessed independently by two reviewers who used the risk of bias table approach (as described in The Cochrane Handbook) which included random sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. The studies were also assessed with the van Tulder 11-item Quality Assessment Scale to obtain a quality score out of 11 (higher scores indicated better quality).

Data extraction
Odds ratios (OR) were calculated for dichotomous data and standardised mean difference were calculated for continuous data, both with 95% confidence intervals (CI). Adverse events were recorded. Participants that withdrew before end of treatment were treated as nonresponders. Authors were contacted for further information if necessary.

Data were extracted independently by two reviewers and disagreements were resolved through discussion and consensus with two more reviewers.

Methods of synthesis
Odds ratios and standardised mean difference with 95% confidence intervals were pooled in random-effects meta-analyses. Heterogeneity was assessed using $X^2$ and $I^2$. Subgroup analyses were performed for class of antidepressant (tricyclic antidepressants and selective serotonin reuptake inhibitors) and sensitivity analyses were undertaken for variations in the definition of depression, reporting of data and risk of bias (i.e. trials scoring above 6/11). Funnel plots were used to investigate possible publication bias.
Results of the review
Twenty-five RCTs were included in the review (1,197 participants; range 12 to 120); 21 were included in the meta-analysis. Five RCTs reported adequate sequence generation, eight had sufficient blinding, 13 had adequate completeness of outcome data. Study duration ranged from four to 52 weeks.

Antidepressant use was associated with significantly better response than placebo at four to five weeks (OR 1.93, 95% CI 1.15 to 3.42; five RCTs), six to eight weeks (OR 2.25, 95% CI 1.38 to 3.67; 12 RCTs) and nine to 18 weeks (OR 2.71, 95% CI 1.50 to 4.91; seven RCTs). Some heterogeneity was indicated at six to eight weeks ($I^2=40\%$) but not at the other time points. Sensitivity analyses showed similar results, except at four to five weeks when excluding trials at high risk of bias and when including trials that used a narrow definition of depression; in these cases no significant treatment effect was observed.

Drop-outs were significantly greater with antidepressants compared with placebo at nine to 18 weeks (OR 2.09, 95% CI 1.02 to 4.31; six RCTs) but were similar at the other time points.

All four studies that reported quality of life outcomes indicated greater improvements with antidepressant than placebo. One of three studies reported significantly greater improvement with antidepressant than placebo.

Dry mouth, nausea, dizziness, sexual dysfunction, hypotension and headache were more likely to be reported with antidepressant than placebo.

The funnel plot was asymmetrical which indicated the possibility of publication bias. Subgroup analyses were reported: tricyclic antidepressants showed a significant effect at all time points whereas selective serotonin reuptake inhibitors only showed a significant effect at nine to 18 weeks.

Authors' conclusions
Antidepressants were effective in treating depression in palliative care but it was possible that efficacy may have been overestimated due to selective reporting and publication biases.

CRD commentary
The research question was supported by inclusion criteria for participants, outcomes and study design and broad criteria for interventions. Several sources of published and unpublished data were searched. The funnel plot indicated the presence of publication bias. It was not reported whether searches were limited by language.

Two reviewers were involved in all stages of the review process which reduced the risk of bias and error. Study quality was assessed using appropriate criteria and taken into consideration in the analysis. It was unclear whether pooling of different drug classes was appropriate, especially considering the results of the subgroup analyses. Possible sources of bias were acknowledged by the authors.

The reliability of the authors' conclusions was unclear as the appropriateness of pooling across drug classes was questionable.

Implications of the review for practice and research
Practice: The authors stated that antidepressants should be considered for treating depression in palliative care. There was insufficient evidence for use of a specific antidepressant; choice of antidepressant should be based on patients' preferences and symptoms, contraindications and potential interactions with other medication.

Research: The authors stated that further research was needed to examine the threshold at which antidepressants have benefit, to determine the impact of antidepressants on function and quality of life, and the relative efficacy and acceptability of specific antidepressants in palliative care.

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