Antidepressants for bipolar depression: a systematic review of randomized, controlled trials

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CRD summary
This review concluded that antidepressants were effective in short-term treatment of bipolar depression. Data did not suggest that switching to mania was a common early complication of antidepressant treatment. The conclusions reflected the evidence presented, but lack of reporting of validity assessment results, small sample sizes for some comparisons and significant statistical heterogeneity for some analyses reduced their reliability.

Authors' objectives
To assess the safety and efficacy of short-term treatment with antidepressants in patients with bipolar depression.

Searching
MEDLINE, EMBASE, CINAHL, PsycLIT, PSYNDEX, LILACS, The Cochrane Library and Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register were searched; search terms were reported. Most databases were searched from inception. The authors checked the reference lists of selected studies, other relevant papers and major textbooks for additional potentially relevant studies. There were no language restrictions.

Study selection
Double-blind randomised controlled trials (RCTs) that compared antidepressants with placebo or alternative drug treatments for patients with bipolar depression were eligible for inclusion. Antidepressants included all tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), noradrenergic reuptake inhibitors, reversible monoamine oxidase inhibitors (MAOIs), bupropion, St John's wort and tryptophan, but not mood stabilisers, anticonvulsants, lamotrigine, sulpiride, benzodiazepines or electroconvulsive therapy. Comparator treatments included mood stabilisers, anticonvulsants and other antidepressants. Participants had to have a current depressive or mixed depressive/manic episode (with or without psychotic symptoms) and at least one previous episode of mania or hypomania (antidepressant-induced mania or hypomania were included). Studies that included both bipolar and non-bipolar patients were included if they randomly assigned bipolar patients separately or if most patients were bipolar. Outcomes of interest were clinical response and remission rates (derived from observer-rated symptom reductions, induction of mania or hypomania and overall dropout rate) as a proxy measure of the acceptability of treatment.

Antidepressant drugs assessed in the included studies were fluoxetine, paroxetine, imipramine, tranylcypromine, deprenyl, moclobemide, desipramine, bupropion, fluvoxamine, clomipramine and amitriptyline. Other types of drug compared with antidepressants were a mood stabiliser, idazoxan and sulpiride. In some of the included studies patients also took olanzapine, lithium, carbamazepine or sodium valproate. Participants in most of the studies were outpatients. All studies excluded patients with a serious physical illness or substance abuse. Patients were aged up to 70 years. Most patients were women. Clinical response was measured with different depression scales.

Two reviewers independently selected the studies. Any disagreements were resolved by discussion with another reviewer.

Assessment of study quality
One reviewer assessed the quality of the included studies based on the randomisation procedure, concealment of treatment allocation, blinding and reporting of withdrawals.

Data extraction
The proportion of patients who responded to treatment and achieved remission, and the rate of switching to mania, were extracted independently by two reviewers. Relative risks (RR) with 95% confidence intervals (CIs) were calculated.

Methods of synthesis
Results were pooled using both fixed-effect and random-effects models. Statistical heterogeneity was assessed using $X^2$ and $I^2$ statistics. Sources of significant heterogeneity were investigated by visual inspection of forest plots to identify outlying results. Sensitivity analyses excluded trials that included non-bipolar patients as well as bipolar patients and by including a trial in which bipolar patients were not randomised separately from non-bipolar patients. Subgroup analyses compared different types of antidepressant drug. The number needed to treat (NNT) was calculated.

Results of the review
Twelve RCTs were included in the review (n=1,088, 1,034 with bipolar disorder, range nine to 456). Five RCTs compared one or more antidepressants with placebo. Four RCTs compared two different antidepressants. Three RCTs compared an antidepressant with another type of medication. Study duration was between four and 10 weeks.

Patients treated with an antidepressant were significantly more likely to respond to treatment than those treated with placebo (random-effects RR 2.29, 95% CI 1.29 to 4.04; four RCTs). There was significant statistical heterogeneity ($I^2=71.4\%$). NNT was 4.2 (95% CI 3.2 to 6.4).

Patients treated with an antidepressant were significantly more likely to reach remission than those treated with placebo (fixed-effect RR 1.41, 95% CI 1.11 to 1.80; two RCTs). There was no evidence of significant statistical heterogeneity. NNT was 8.4 (95% CI 4.8 to 33). There was no significant difference between antidepressant treatment and placebo in switching to mania. Dropout rates were significantly higher for patients treated with placebo than those treated with an antidepressant (fixed-effect RR 0.71, 95% CI 0.58 to 0.88). Sensitivity analysis did not significantly alter the findings.

There was no significant difference in response to treatment or remission rates between tricyclic antidepressants and other antidepressants. Tricyclic antidepressants caused more switching to mania than other antidepressants (fixed-effect RR 2.92, 95% CI 1.28 to 6.71; six RCTs). There was no significant difference in dropout rates between tricyclic antidepressants and other antidepressants. Sensitivity analysis did not significantly alter the findings.

There was insufficient data to pool studies that compared antidepressants with other types of medication.

Authors’ conclusions
Antidepressants were effective in short-term treatment of bipolar depression. Clinical trial data did not suggest that switching to mania was a common early complication of treatment with antidepressants. It may be prudent to use a selective serotonin reuptake inhibitor or a monoamine oxidase inhibitor as a first-line treatment instead of a tricyclic antidepressant.

CRD commentary
The review addressed a clearly defined question. A number of sources were searched for potentially relevant studies. Limited attempts were made to identify unpublished studies and potential for publication bias was not assessed. Study selection and data extraction were undertaken independently by two reviewers, which reduced potential for reviewer bias and error. Validity assessment was undertaken based on appropriate criteria; however, the validity assessment results of the were not reported and did not appear to have been used in the analyses. Appropriate methods were used to pool the results and to assess heterogeneity. For most analyses only fixed-effect results were reported, despite the presence of significant statistical heterogeneity for some results. Some of the comparisons were based on small numbers of studies and sample sizes, and confidence intervals were wide when comparing different types of antidepressant drug.

The authors’ conclusions reflected the evidence presented and appeared appropriate. However, the lack of reporting of validity assessment results, the small number of included studies and sample sizes for some comparisons and significant statistical heterogeneity for some of the analyses reduced the reliability of the conclusions. It should be noted that many participants in the included studies were also taking other medications for bipolar depression.

Implications of the review for practice and research
Practice: The authors stated that there was no strong reason to avoid antidepressants for patients with bipolar depression. For patients already taking a mood stabiliser, they advised adding an antidepressant as a first-line treatment.

Research: The authors stated that future studies of antidepressant treatment for bipolar depression should pay more
attention to the definition, follow-up and reporting of manic symptoms. They also suggested that large studies should be undertaken to assess the efficacy of mood stabilisers, looking at the long term outcome of depression, quality of life and focus on duration of remission as well as response. A number of other suggestions for further research were made.

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