Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis

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CRD summary
The review found that based on the limited available evidence, antidepressants did not appear effective for acute treatment of bipolar depression compared with other medications or placebo. Antidepressants did not appear to increase the risk of affective switch. The overall conclusions appear justified, although their clinical utility was limited by a lack of high quality studies.

Authors' objectives
To evaluate the efficacy and safety of antidepressants for acute treatment of bipolar depression.

Searching
EMBASE, MEDLINE, CINAHL, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL) and databases of trial registries were searched from 2003 to August 2009. Search terms were reported. A previous systematic review of studies published between 1980 and 2004 (see Other Publications of Related Interest) was checked for earlier studies. Reference lists of selected article and reviews were checked for further studies. The search was not restricted by language.

Study selection
Double-blinded randomised controlled trials (RCTs) of up to 16 weeks' acute antidepressant treatment (included adjunctive or monotherapy and fixed- or flexible-dose) compared to an active drug or placebo for adults with bipolar I or II disorder (or a co-occurring mixed state) who were experiencing a current depressive state were eligible for inclusion. The primary review outcomes were clinical response and remission (measured by magnitude of symptom reduction on established diagnostic scales) and safety (affective switch to mania or hypomania). The secondary outcome was treatment tolerability (drop-outs for any reason). Studies that included a minority of participants without bipolar depression were eligible if data were analysed separately.

Participants in the included studies were 18 to 71 years old. Most participants were women (mean 61%) and most were outpatients. Nearly half of the studies reported participants with either bipolar I or bipolar II disorder and some only included participants with bipolar I disorder. About one third of the studies reported participants with a history of rapid cycling. Participants received a wide range of antidepressants in various doses; these included bupropion, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and tricyclics. In most studies all participants received concomitant medication such as lithium, valproate or carbamazepine. Controls received placebo, other medication (such as lamotrigine, lithium, divalproex) or other antidepressants. Depression measures and outcome definitions varied widely across studies. Study duration was mostly four to eight weeks (range six to 26 weeks). Only data up to 16 weeks were included in the review. More than half of the studies (and most of the studies with placebo controls) were pharmaceutical industry funded. Nearly half of the studies were conducted across multiple sites.

The authors did not state how many reviewers performed the selection. Any uncertainty over inclusion was discussed between authors.

Assessment of study quality
Methods of blinding, randomisation, allocation concealment and reporting of withdrawals were each rated as adequate, unclear or inadequate.

Two blinded researchers conducted the assessment and resolved discrepancies by discussion.

Data extraction
Risk ratios (RRs) with 95% confidence intervals (CIs) were extracted or calculated from the number of events in the control and intervention groups of each study. Data were estimated from graphs in the articles where necessary. An
intention-to-treat approach was used. An unfavourable outcome for drop-outs was assumed. Last observation carried forward data were used where reported. Participants who received at least one follow-up assessment were analysed for efficacy and safety outcomes.

Two reviewers independently extracted data and resolved any discrepancies through discussion. Attempts were made to contact authors for more information where necessary.

**Methods of synthesis**

Studies were pooled to calculate pooled risk ratios and 95% CIs using a fixed-effect model. Heterogeneity was assessed with the $Q$ and $I^2$ statistics. Where there was significant heterogeneity, study quality was considered and a sensitivity analysis that excluded outliers was conducted. In other sensitivity analyses, analysis was limited to placebo-controlled studies that met all quality criteria, those with participants with bipolar I disorder only, studies that included participants with rapid cycling, studies in which all participants did or did not receive a mood stabiliser and studies without pharmaceutical industry connections.

**Results of the review**

Fifteen RCTs (2,373 participants, range 15 to 833) were included. Methods of randomisation and allocation concealment were adequate in four studies, as was blinding in 10 studies and reporting of withdrawals in 12 studies. In the other studies these factors were unclear or inadequate.

There was no significant difference between antidepressants and placebo in rates of clinical response (five RCTs, $I^2=69$%), remission (four RCTs, $I^2=51$%) and affective switch (six RCTs, $I^2=0$%). Similarly, there was no significant difference between antidepressants and other medications in rates of clinical response (four RCTs, $I^2=19$%), remission (two RCTs, $I^2=0$%), affective switch (three RCTs, $I^2=0$%) and tolerability (five RCTs).

When antidepressants were compared head-to-head, there was no significant difference in rates of clinical response between bupropion and other antidepressants (venlafaxine, sertraline, desipramine and idazoxan) (three RCTs) and between moclobemide and imipramine (one RCT). One RCT reported higher rates of clinical response with tranylcypromine than with imipramine (75% versus 36%) but affective switch rates were comparable.

When bupropion was compared with other antidepressants (sertraline, venlafaxine, desipramine) for affective switch rates, the risk was significantly lower in the bupropion group (RR 0.34, 95% CI 0.13 to 0.88; two RCTs, $I^2=0$%). There was no significant difference between bupropion and other antidepressants in tolerability (two RCTs).

Findings of subgroup and sensitivity analyses were reported.

**Authors' conclusions**

Based on the limited evidence available, antidepressants did not appear effective for acute treatment of bipolar depression compared with other medications or placebo. Antidepressants did not appear to increase the risk of affective switch.

**CRD commentary**

The objectives of the review were clear. Relevant sources were searched for studies without restrictions on language and publication status. Two unpublished trials were excluded due to lack of data, which suggested a risk of publication bias that did not appear to be assessed formally. Risks of reviewer bias and error were minimised by having two reviewers independently extract data and conduct validity assessment. It appeared that more than one reviewer independently selected the studies (not stated explicitly).

It was unclear why a fixed-effect model was used to combine the studies when there was heterogeneity between them. In two of the analyses of bupropion versus other antidepressants some participants were double counted and this reduced confidence in the findings of these analyses. Measures of statistical significance were not reported for all outcomes. Methods used to assess and explore heterogeneity appeared appropriate. The authors noted that the review was limited by differences between the studies (such as in outcome definitions and drug doses), there were relatively few studies and study quality was suboptimal.
The authors' overall conclusions appear justified, although their clinical utility is limited by a lack of high quality studies.

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

**Practice:** The authors stated that antidepressants did not appear effective for acute treatment of bipolar depression in adults but clinicians should continue to consider their use on a case-by-case basis until more evidence was available.

**Research:** The authors stated a need for further research to determine whether antidepressants were effective for treating depression in some subgroups of people with bipolar depression (such as those with bipolar II disorder or minimal history of affective switch). Future studies should take account of the ratio of participants with bipolar I versus bipolar II disorder as this may influence the switch rate.

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