Efficacy and acceptability of mood stabilisers in the treatment of acute bipolar depression: systematic review

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CRD summary
This review found that mood stabilisers had moderate efficacy in achieving clinical response and remission in patients with acute major depression. A lack of information about follow-up in the patients made it difficult to judge the reliability of the authors' conclusions and these should be interpreted with caution.

Authors' objectives
To compare the efficacy, safety and acceptability of mood stabiliser monotherapy with combination therapy of mood stabilisers and antidepressant treatment in adults with acute bipolar depression.

Searching
MEDLINE, EMBASE, CINAHL, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews were searched to January 2008 for relevant studies in any language; search terms were reported. Tables of contents of journals were monitored up to 1 April 2008 for additional studies. Reference lists of retrieved articles and the ClinicalTrials.gov were searched.

Study selection
Published randomised controlled trials (RCT) described as double-blind that evaluated mood stabiliser treatments in adults aged 18 to 65 years with bipolar disorder in the stage of acute major depression (defined in the review) were eligible for inclusion if they attained a score of 3 points or more on the Jadad scale. Placebo-controlled trials and trials that used an active comparator were included. Studies with diagnostically heterogeneous populations needed to report data separately for people with bipolar disorder. Trials that evaluated lithium, valproic acid, carbamazepine, lamotrigine, topiramate, gabapentin, benzodiazepines and typical and atypical antipsychotics were eligible if the medications were commenced during the depressive phase of bipolar disorder. Crossover trials and trials that examined patients in mixed states were excluded.

Most patients were diagnosed with bipolar disorder type I. Mood stabiliser monotherapy was compared with placebo and with combination therapy of mood stabiliser and other pharmacological agents (antidepressants). Mood stabilisers were lamotrigine, carbamazepine, valproic acid, olanzapine and quetiapine. One study also used a psychosocial intervention. Outcomes were response rates, remission, affective switching, suicidal behaviour and clinically significant weight gain. All-cause discontinuation was used as a proxy for the acceptability of treatment for individuals.

Two reviewers independently performed the study selection. Any disagreements were resolved by discussion or referral to a third reviewer.

Assessment of study quality
Methodological quality was evaluated using the 5-point Jadad scale of randomisation, blinding, description of withdrawals and dropouts. This assessment was performed as part of the study selection. The reviewers assessed whether analyses in the studies were conducted on an intention-to-treat basis.

It was unclear how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted data to calculate relative risks (RR) and corresponding 95% confidence intervals (CIs) for the outcomes. Authors of trials were contacted in the event of missing data. Any disagreements were resolved through discussion or referral to a third reviewer.
Methods of synthesis
Pooled relative risks and 95% CIs were calculated using a DerSimonian and Laird random-effects model. Statistical heterogeneity was evaluated by Cochran's Q-statistic, I² and visual appraisal of forest plots. In the event of statistical heterogeneity, post hoc subgroup analyses were undertaken to explore potential sources of heterogeneity. Numbers need to treat and harm were calculated where relative risks were statistically significant.

A priori sensitivity analyses were conducted using placebo-controlled trials only and were conducted to explore differences in terms of medication types, antipsychotic and anticonvulsant classes, bipolar type, gender and patients with psychotic features or a rapid cycling course of illness. Publication bias was assessed using funnel plots where there were more than 10 studies.

Results of the review
Eighteen RCTs (4,105 participants) were included in the review. Trial duration ranged from three to 26 weeks; most trials lasted between six and eight weeks. There were high rates of drop-outs in both groups in the trials.

Twelve studies reported data that compared mood stabiliser monotherapy to placebo. There were significant benefits observed with mood stabiliser monotherapy compared to placebo in clinical response (RR 1.30, 95% CI 1.16 to 1.44, NNT=10; 10 trials, n=2,864) and symptom remission (RR 1.51, 95% CI 1.27 to 1.79, NNT=8; four trials, n=1,709).

There was an increased risk of weight gain with mood stabiliser therapy compared to placebo (RR 6.11, 95% CI 1.43 to 26.07, NNH=11; three trials). There was statistically significant heterogeneity for this outcome, which was explained by medication type as there was increased rates of weight gain in trials that evaluating olanzapine.

There were no significant differences observed between mood stabiliser therapy and placebo in acceptability, likelihood of undergoing an affective switch, and suicidal behaviour.

There were no statistically significant differences observed between mood stabiliser monotherapy and combination therapy of mood stabilisers and antidepressants in clinical response (five trials, n=1,305), symptom remission (four trials, n=1,212), acceptability and safety. There were no differences by medication or medication class for any outcome. There was statistically significant heterogeneity reported for the clinical response outcome (I²=67.5%). This was reported as due to the different methodology employed in one study that used a psycho-social intervention.

Comparisons of mood stabiliser monotherapy and antidepressants showed no significant differences in clinical response or remission rates (two trials, n=39), acceptability (three trials, n=77) and affective switch.

Visual appraisal of the funnel plots showed that publication bias was unlikely for clinical response (mood stabiliser compared to placebo).

Authors' conclusions
The results of this review supported use of mood stabilisers as first line treatments for patients with acute bipolar depression. The modest effect sizes observed in studies of each class of medication suggested that optimising or combining currently available medications was unlikely to eliminate morbidity associated with this phase of illness.

CRD commentary
The review addressed a clearly defined question. Criteria for inclusion of studies were clearly stipulated. Appropriate databases were searched for studies. There were some attempts to identify unpublished studies. The authors acknowledged that there was still potential for publication bias. There were no language restrictions. Steps were taken by the reviewers to minimise errors and bias at all stages of the review process. Studies were included if they attained a certain level in the validity assessment. Although the reviewers assessed quality and stated that there were serious limitations of the results because of high drop-out rates, no full assessments of the included studies were reported. Little information was provided on doses and drug regimens in the treatment groups. There was only a small number of trials for each medication type. Follow-up duration was typically short. There were small numbers of events reported in the trials. The authors stated that their decision to pool the results of the studies may be justified on the basis of few differences in medications and the presence of minimal heterogeneity. The different medications and class of
medications were not compared directly in the review. The lack of information on patients, treatments and follow-up made it difficult to judge whether pooling of the studies was appropriate.

Support and honoraria from Wyeth, AstraZeneca, Janssen, Lilly, Novartis, GlaxoSmithKline, Boehringer, Oryx and Lundbeck were noted.

A lack of information on losses to follow-up and on patients and treatments made it difficult to draw conclusions about the reliability of the authors' conclusions; these should be interpreted with some caution.

Implications of the review for practice and research

Practice: The authors stated that most participants in the included trials had bipolar type I depression and it was unknown what effects the treatments would have in patients with Type II bipolar disorder.

Research: The authors stated that there were few direct comparisons of mood stabiliser therapy with antidepressant treatment in bipolar depression. More research was required to determine optimal use of both treatments.

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