CRD summary
This review examined the efficacy of agents for treating and preventing manic and depressive symptoms of bipolar disorder, to identify those meeting the authors' definition of 'mood stabiliser'. The authors concluded that only lithium met their criteria. As the methods of analysis were simplistic and there were significant gaps in the evidence base, this conclusion may not be reliable.

Authors' objectives
To review the literature on the efficacy of agents for treating and preventing manic and depressive symptoms of bipolar disorder, to identify which agents best meet their definition of 'mood stabiliser'.

Searching
MEDLINE, PsycLIT and the Cochrane CENTRAL Register were searched for papers published in English in peer-reviewed journals. Experts in the field were contacted and reference lists were checked to locate further studies.

Study selection

Controlled trials of any design were eligible for inclusion in the review. The sample size was required to be at least 4.

Specific interventions included in the review
Any pharmacological agents used for treating bipolar disorder were eligible for inclusion. Studies on a variety of drugs (lithium, carbamazepine, valproate, lamotrigine, neuroleptics, benzodiazepines, calcium-channel blockers, antidepressants and other miscellaneous agents) were included in the review. Also included were studies of ECT (not defined; presumably electroconvulsive therapy) and of a low-vanadium diet. Studies involving combination therapies were excluded from the review.

Participants included in the review
Studies of people with bipolar disorder, or where the results were reported separately for a subgroup of participants with bipolar disorder, were eligible for inclusion. The included studies were of in-patients and out-patients; no further details were reported. Two trials included only subsets of bipolar disorder: those with rapid recycling and those with co-morbid borderline personality disorder.

Outcomes assessed in the review
The studies were required to report specified quantitative outcomes. The outcomes assessed in the review were those relating to the four roles of a mood stabiliser: treatment of manic symptoms, treatment of depressive symptoms, prevention of manic episodes, and prevention of depressive episodes.

How were decisions on the relevance of primary studies made?
The authors did not explicitly state how the papers were selected for the review, or how many reviewers performed the selection. However, two independent reviewers appear to have classified the studies according to the study design.

Assessment of study quality
The quality of the studies was not explicitly assessed, although details of blinding were extracted.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data
extraction.

The results of the studies were categorised as either positive or negative, with statistical significance set at a P-value of less than 0.05. Further details of this were provided in the report.

Methods of synthesis
How were the studies combined?
The results were tabulated, grouped by intervention. Further tables summarised evidence for agents examined by at least two studies, grouped by study design, and these were combined in a narrative. There were three levels of analysis:

a primary analysis where agents were considered to be efficacious if supported by at least two placebo-controlled trials with positive findings;

a sensitivity analysis with stricter criteria, where agents were considered to be efficacious if supported by at least two placebo-controlled, parallel-group design trials with positive findings; and

a sensitivity analysis with more relaxed criteria, where agents were considered to be efficacious if supported by at least two placebo-controlled or active-controlled trials.

How were differences between studies investigated?
Sensitivity analyses were performed to investigate the influence of study design on the summary results.

Results of the review
The review included 81 studies (79 actually listed in the review) involving approximately 4,330 participants. There were 59 randomised controlled trials (RCTs; 4,013 participants) and 20 studies of a within-subjects (crossover) design (317 participants).

Primary analysis (agents considered efficacious if supported by at least two placebo-controlled trials with positive findings).

Mania treatment: lithium, valproate, olanzapine and verapamil each met criteria for efficacy, although the two positive trials of verapamil were very small; one larger trial found negative results for verapamil.

Depression treatment: only lithium met the criteria for efficacy.

Mania and depression prophylaxis: lamotrigine met the efficacy criteria for prophylaxis, although relapse polarity was not considered in either of the supporting trials; lithium was supported by five trials examining relapse to either episode, two trials on mania and two trials on depression. Two further trials found negative results for lithium.

Lithium was the only agent that could be classed as a mood stabiliser as it had efficacy in all four roles. The inclusion of studies with active controls in the analysis did not identify any further mood stabilisers.

Sensitivity analyses.

The analysis of only placebo-controlled studies with parallel-group design led to no agents being identified as mood stabilisers. The analysis where agents were considered to be efficacious if supported by at least two placebo-controlled or active-controlled trials found only lithium was classed as a mood stabiliser.

Authors' conclusions
When all four treatment roles were considered, the evidence supported lithium as a mood stabiliser for the treatment of bipolar disorder.
CRD commentary
This review addressed a clear question with broadly defined inclusion criteria. The search incorporated a number of relevant databases and strategies, but its restriction to published English-language studies might have introduced language and publication biases. It was unclear whether steps were taken to minimise errors and bias in other stages of the review process, as the methods were not reported in sufficient detail. The quality of the included studies was not assessed, the studies being divided simply into placebo-controlled, active-controlled, and placebo-controlled parallel-group design (the latter being considered the best quality).

The methods used to combine the studies were clearly explained, and the authors discussed limitations of the approach taken in the review. The review encompassed a huge amount of data and attempted to synthesise it in a pragmatic way. However, as the methods of analysis were rather simplistic and study validity was not fully considered, the conclusion may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that their analysis supported a role for lithium as first-line treatment for bipolar disorder.

Research: The authors did not explicitly state any implications for research, but implied that there were significant gaps in the evidence base.

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