Systematic overview of lithium treatment in acute mania

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Authors' objectives
To evaluate the efficacy of lithium in the treatment of acute mania.

Searching
MEDLINE, EMBASE and Science Citation Index were searched from 1966 to the end of June 1999 were searched in addition to the Cochrane Library (Issue 1, 1999). MeSH terms were: 'lithium', 'bipolar disorder' and 'clinical trial'. This was followed by a textword search using 'mania' and 'acute treatment'. Reference lists of RCTs, narrative and systematic reviews were also searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs). The included studies were double blind, parallel group design; either single or double blind crossover; or open trials.

Specific interventions included in the review
Lithium (dosage not stated). The control was either placebo or active treatment (chlorpromazine, haloperidol, carbamazepine, valproate, verapamil, risperidone or clonidine). Treatment periods ranged from 20 days to 6 weeks.

Participants included in the review
Participants with mania. Inclusion criteria in the studies were participants who had American Psychiatric Association criteria (DSM-111, DSM-IV or DSM-III-R) for bipolar disorder, manic episode, Mayer-Gros criteria for manic depressive illness, Research Diagnostic Criteria (RDC) criteria for mania, or bipolar disorder.

Outcomes assessed in the review
The differences in the reduction in mania severity scores, and the ratio and difference in improvement response rates. The Brief Psychiatric Rating Scale (BPRS) was the most widely used metric scale, whereas the Clinical Global Impression (CGI) was the most widely used global scale.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
Data were abstracted independently by two reviewers and disagreement resolved by discussion. The data abstracted were the year of publication, study design (double- or single-blind, crossover or parallel), rating scales, duration of the study, sample characteristics, sample size, severity scores and response rates. In addition, the incidence of any side effects was also recorded.

Methods of synthesis
How were the studies combined?
Pooled standard deviations between lithium and control treatment were calculated first, and the standard error of the difference was then obtained from this pooled estimate. The inverse of the squared standard error of the difference in
response between lithium and control treatment was used as the weight. The same approach was used for both the BPRS and the CGI. Efficacy was also estimated in the rate ratio. In the pooling of the rate ratios, the individual log rate ratio weighted by the inverse of the variance was used. The number needed to treat was calculated from the pooled rate difference.

How were differences between studies investigated?
A random-effects model was used where the results were considered heterogeneous on the basis of the Q-statistic for heterogeneity (0.05 level of significance).

Results of the review
Twenty-two trials were included in a detailed analysis. A total of 658 patients from 12 trials were pooled.

The response rate ratio for lithium against placebo was 1.95 (95% CI: 1.17,3.23). The mean number needed to treat was five (95% CI: 3, 20). Patients were twice as likely to obtain remission with lithium than with chlorpromazine (rate ratio = 1.96, 95% CI: 1.02, 3.77). The mean number needed to treat was four (95% CI: 3, 9). Neither carbamazepine nor valproate was more effective than lithium. The response rate ratios were 1.01 (95% CI: 0.54, 1.88) for lithium compared to carbamazepine and 1.22 (95% CI: 0.91, 1.64) for lithium against valproate. Haloperidol was no better than lithium on the basis of improvement based on assessment of global severity. The differences in effects between lithium and risperidone were -2.79 (95% CI: -4.22,-1.36) in favour of risperidone with respect to symptom severity improvement and -0.76 (95% CI: -1.11,-0.41) on the basis of reduction in global severity of disease. Symptom and global severity was as well controlled with lithium as with verapamil. Lithium caused more side-effects than placebo and verapamil, but no more than carbamazepine or valproate.

Authors' conclusions
Lithium is more effective than placebo and chlorpromazine. Carbamazepine, valproate and verapamil were no better than lithium, either in terms of response rate or reduction in severity of illness. Lithium was associated with more acute adverse effects than placebo and verapamil, but no more than carbamazepine nor valproate. It is our view that, based on estimates of efficacy, lithium should remain the first line of treatment for acute mania.

CRD commentary
This is a reasonable review with clear inclusion criteria. An adequate search strategy was undertaken but there was no attempt made to locate unpublished studies. Thus there is a possibility of publication bias. The validity of the trials was not assessed. However, good information about the included trials was provided. The number of patients included in the trials which were pooled was small (total = 658) and there were several comparisons. Thus the conclusions are not fully supported by the evidence included in the review. For example, the conclusion that lithium is more effective than placebo was mainly based on the results of one trial. Given the other limitations of the review outlined above, the conclusions should be viewed with caution.

Implications of the review for practice and research
Practice: The authors state that the clinical trial evidence suggests that lithium should remain the first-line treatment for acute mania.

Research: The authors do not state any implications for research.

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