Magnitude of effect of lithium in short-term efficacy studies of moderate to severe manic episode


CRD summary
This review assessed the effect size of lithium in short-term efficacy studies of moderate to severe manic episodes and concluded that lithium was effective. The reliability of the conclusion was unclear given the limitations of the review in terms of the literature search, reporting and possible methodological weaknesses.

Authors’ objectives
To evaluate the effectiveness of lithium in the short-term treatment of people with moderate to severe manic episode.

Searching
MEDLINE and Embase were searched to March 2006 to identify relevant studies. Search terms were reported. Registration files submitted by pharmaceutical companies to the Dutch Medicines Evaluation Board between 1997 and 2005 were searched for published and unpublished studies.

Study selection
Randomised placebo controlled trials of participants with moderate to severe manic episode treated with lithium (including studies submitted to the Medicines Evaluation Board where lithium represented a third study arm) were eligible for inclusion in the review. Participant diagnoses were based on the Research Diagnostic criteria (RDC) for manic episode and Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). All participants were hospitalised at the beginning of the study. All studies reported the administration of concomitant psychoactive medication.

The outcome inclusion criteria were unspecified, but the primary outcome measure was severity score at baseline and on day 21 as measured using either the Young Mania Rating Scale (YMRS) or the Mania Rating Scale 11 (MRS-11) derived from the Schedule for Affective Disorders and Schizophrenia-Change version (SADS-C).

The authors stated neither how the studies were selected for the review nor how many reviewers performed the selection.

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

Data extraction
Data were extracted on a modified intention to treat basis, which included all randomised patients who took at least one dose of study medication and had at least one post-baseline efficacy assessment. This was in order that Cohen’s standardised effect size, responders rate difference (responders were defined as patients who achieved a reduction of greater than or equal to 50%) and 95% confidence intervals (CI) could be calculated.

The authors stated neither how the data was extracted for the review nor how many reviewers performed the extraction.

Methods of synthesis
Standardized effect differences and responder rate differences were separately combined in meta-analyses using the DerSimonian and Laird random effects model. Heterogeneity was assessed using the \( \chi^2 \) test. The last observation was carried forward in the case of missing values. Sensitivity analysis was performed by the exclusion of one study that showed a lack of assay sensitivity.
Results of the review
Six randomised placebo controlled trials were included in the meta-analyses (n=1,032). The sample sizes ranged from 107 to 226. Drop out rates varied from 14% to 63% in the lithium arm and 13% to 65% in the placebo arm.

An overall medium effect size of 0.40 (95% CI: 0.28 to 0.53) was determined. There was no evidence of statistically significant heterogeneity. The overall difference in response rate between lithium and placebo was 17% (95% CI 0.08 to 0.26) and there was no evidence of statistically significant heterogeneity. The number of patients needed to be treated for one patient to benefit was approximately six (95% CI 3.8 to 12.5). The statistical significance of these findings was unclear.

When the one study that showed a lack of assay sensitivity was removed from the analysis, the overall difference between lithium and placebo became 20% and the number needed to treat became five. There was a large variation in the improvement observed in the placebo group.

Authors' conclusions
Lithium was effective in the treatment of moderate to severe manic episodes.

CRD commentary
The review addressed a clear question. The search was limited to two databases, but efforts were made to find unpublished studies by searching the registration file submissions to the Medicines Evaluation Board. The inclusion and exclusion criteria were clear with the exception of outcome measures. It was not reported how study selection and data extraction were performed, so reviewer bias and error might have been introduced. The inclusion criteria stipulated placebo controlled randomized trials, but it was not reported whether or not a formal assessment of validity was performed, therefore, the potential impact of methodological flaws of the studies upon the reliability of the findings could not be assessed. Appropriate methods were used to pool the results and to investigate statistical heterogeneity. The reliability of the authors' conclusion was unclear given the limitations of the review in terms of literature search, reporting and possible methodological weaknesses of the review.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The large variation in improvement observed in the placebo group meant that a placebo control in this type of study was indispensable.

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