**CRD summary**

This review evaluated the efficacy of lithium in accelerating and augmenting the clinical response of patients with depression. The authors concluded that lithium was an effective augmentation strategy. However, their conclusion may be strong given the small sample sizes of the included studies, lack of a validity assessment and poor reporting of review methodology.

**Authors' objectives**

To evaluate the efficacy of lithium in accelerating and in augmenting the clinical response of patients with depression.

**Searching**

MEDLINE (1966 to July 2006), EMBASE (1989 to July 2006), and the Cochrane CENTRAL Register (Issue 3, 2006) were searched; the search terms were reported. In addition, the references of identified studies and published reviews were checked. There were no language restrictions. For the augmentation meta-analysis, the databases were only searched from June 1997 since the authors had already conducted a meta-analysis on this subject and databases had been searched up to June 1997 (see Other Publications of Related Interest).

**Study selection**

**Study designs of evaluations included in the review**

Double-blind, placebo-controlled randomised controlled trials (RCTs) were eligible for inclusion.

**Specific interventions included in the review**

Studies in which patients were treated with any antidepressant plus lithium in any dose or with placebo were eligible for inclusion. The patients in the included acceleration studies were treated with clomipramine, maprotiline, tianeptine, amitriptyline, desipramine, or various tricyclic antidepressants. The doses of lithium given in addition to these antidepressants were 750 to 900 mg each day or a serum level of 0.7 to 1.3 mmol/L. The duration of treatment ranged from 3 to 6 weeks. The patients in the included augmentation studies were treated with citalopram, nortriptyline, various antidepressants, or various tricyclic antidepressants alone or in conjunction with tetracyclines, monoamine oxidase inhibitors or selective serotonin re-uptake inhibitors. Where stated, the duration of treatment ranged from 2 to 42 days.

**Participants included in the review**

Patients with unipolar or bipolar disorder, depressive phase, were eligible for inclusion. For inclusion in the acceleration meta-analysis, studies had to include only patients that had not previously had appropriate treatment for the depressive episode. For inclusion in the augmentation meta-analysis, studies had to include only patients unresponsive to conventional antidepressants. The participants in the included studies were male and female, mean age 37 to 54 years (where stated), with unipolar and bipolar disorder.

**Outcomes assessed in the review**

Studies that used an accepted criterion for depressive episodes and reported outcomes in a clear, dichotomous classification and/or with a valid depression scale were eligible for inclusion. The primary outcome for the acceleration meta-analysis was the change in depression scale rating at 1 to 2 weeks after treatment. The primary outcome for the augmentation meta-analysis was the odds ratio (OR) of patients responding. Included lithium acceleration studies assessed depression using the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery-Asberg Depression Rating Scale at days 7, 11 and 14. Included lithium augmentation studies assessed the change in HAM-D score and change in Short Clinical Rating Scale.

**How were decisions on the relevance of primary studies made?**

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For the acceleration studies, standardised differences between the ratings scales of the placebo and lithium groups were calculated using Hedges’ adjusted $g$. For the augmentation studies, ORs of patients responding to treatment were extracted from the last measurement provided. Authors were contacted for missing data or, if this was not possible, data were extracted from figures and/or estimated assuming the largest standard deviation for the statistical significance.

Methods of synthesis
How were the studies combined?
Standardised mean differences were pooled in a random-effects meta-analysis (DerSimonian and Laird model) for the acceleration studies. ORs were pooled in a fixed-effect meta-analysis for the augmentation studies. Publication bias was assessed using Egger’s test.

How were differences between studies investigated?
Differences between the studies were investigated using the chi-squared test for statistical heterogeneity.

Results of the review
Five acceleration studies (n=231) and 10 augmentation studies (n=269) were included. All were RCTs.

Acceleration studies.
There was no statistically significant difference between lithium and placebo in terms of acceleration of response to treatment. The authors stated that statistical heterogeneity was present ($p<0.07$). There was no evidence of publication bias.

Augmentation studies.
Lithium was associated with a statistically significant augmentation of response to treatment compared with placebo (OR 3.11, 95% confidence interval: 1.80, 5.37, $p<0.0001$). The mean response rate was 41.2% in the lithium group and 14.4% in the placebo group. The number of patients that would need to be treated for one patient to benefit is 5. There was no evidence of statistical heterogeneity or publication bias.

Authors’ conclusions
This review supports previous evidence that lithium is an effective augmentation strategy. However, there was only modest evidence that lithium accelerates the response to antidepressants.

CRD commentary
The review question was stated clearly and inclusion criteria were clear in terms of the intervention, participants, outcomes and study design. Three appropriate databases were searched without any language restrictions. The authors made no attempts to identify unpublished studies, although publication bias was assessed and no evidence of it was found. However, with such a small number of included studies (particularly acceleration studies), an assessment of publication bias was unlikely to provide a reliable estimate. The authors did not report how the studies were selected or how the data extracted, so it is not known whether any steps were taken to reduce the possibility of error and bias in the review process. The authors did not state that they assessed the validity of the primary studies, thus the quality of them is not known. Study sample sizes were small. Heterogeneity was investigated, but the acceleration studies were combined despite the presence of statistically significant heterogeneity; combining these studies in a meta-analysis might not have produced reliable results. The authors’ conclusions may be strong when considering the small sample sizes of the included studies, lack of a validity assessment and poor reporting of review methodology.
Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: It would be of theoretical and clinical interest to investigate lithium augmentation with a selective noradrenergic antidepressant compared with a selective serotonergic antidepressant. A double-blind RCT that controls for the effect of lithium alone is also warranted.

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Other publications of related interest

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.