Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis

Cipriani A, Hawton K, Stockton S, Geddes JR

CRD summary
This updated review concluded that lithium was effective in reducing the risk of suicide in people with mood disorders such as depression and bipolar disorder. The conclusion reflects the evidence presented and is likely to be reliable.

Authors' objectives
To update a previous review that assessed the effectiveness of lithium in preventing suicide and self harm in people with mood disorders.

Searching
MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to January 2013. Search terms were reported. No language restrictions were applied. Trial databases of regulatory authorities and clinical trial registries were searched as were websites of drug manufacturers.

Study selection
Randomised controlled trials (RCTs) that compared lithium with placebo or another compound in the long-term (>12 weeks) treatment of mood disorders were eligible for inclusion. Participants could be adults or children diagnosed with unipolar depression, bipolar disorder, schizoaffective disorder, dysthymia or rapid cycling disorder. The main outcomes were suicide, deliberate self-harm and all-cause mortality. Studies that recruited participants with a serious concomitant medical disorder were excluded.

Some included trials recruited only patients with unipolar depression or bipolar disorder; others included a mix of participants with different disorders. Treatment setting and stage of disease varied widely across trials. Lithium was compared with placebo and 14 other treatments in trials with up to four arms. Other drugs were given in most trials (details in the paper).

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Study quality was assessed by two independent reviewers using Cochrane risk of bias criteria.

Data extraction
Data were extracted to calculate odds ratios (OR) and associated 95% confidence intervals (CI) using Peto's method. Intention-to-treat data were used where possible. Study authors or sponsors were contacted for additional data where necessary.

Data extraction was performed by two independent reviewers.

Methods of synthesis
Pooled Peto odds ratios and 95% CI were derived by meta-analysis. Different head-to-head comparisons were analysed separately. Heterogeneity was assessed visually and using the $I^2$ and $X^2$ statistics. Preplanned sensitivity analyses focused on studies in people with unipolar depression and on studies recruiting children and young people aged under 18.

Results of the review
Forty-eight RCTs (6,674 patients) were included. Mean follow-up was 19.1 months (range four to 48 months). Study quality was generally good but some trials did not report details of randomisation and allocation concealment. Twenty-nine trials had fewer than 100 participants, resulting in few suicide or self-harm events.
Compared with placebo, lithium significantly reduced suicide (Peto OR 0.13, 95% CI 0.03 to 0.66; four RCTs) and all-cause mortality (Peto OR 0.38, 95% CI 0.15 to 0.95; eight RCTs) but there was no significant difference for self-harm (Peto OR 0.60, 95% CI 0.27 to 1.32; three RCTs). Heterogeneity was not significant.

Differences between lithium and active comparators for suicide and all-cause mortality were not significant. Lithium reduced deliberate self-harm compared with carbamazepine (Peto OR 0.14, 95% CI 0.02 to 0.83) but not other drugs. Heterogeneity was generally low.

In sensitivity analyses against placebo, lithium reduced suicide and all-cause mortality but not self harm in patients with unipolar depression. The planned analysis focusing on young people was not possible because of small numbers of events.

**Authors’ conclusions**
Lithium was an effective treatment for reducing the risk of suicide in people with mood disorders.

**CRD commentary**
The review question and inclusion criteria were clear. The search was thorough and included attempts to locate unpublished and ongoing trials. Study selection, quality assessment and data extraction were performed by two reviewers which minimising risk of errors or bias. Study quality was assessed using standard criteria for RCTs and was considered generally good (despite some reporting limitations).

Standard methods were used for meta-analysis. The large number of comparisons meant that numbers of trials and events were small for some analyses. Statistical heterogeneity was assessed and some sensitivity analyses were performed.

Overall this was a well-conducted review and the authors’ main conclusion is likely to be reliable. The small numbers of events and wide confidence intervals suggest some uncertainty around the magnitude of the effect of lithium on suicide.

**Implications of the review for practice and research**

**Practice:** The authors stated that lithium should continue to have an important clinical role in treatment of mood disorders. Significant adverse effects (not considered in the review) mean that clinical decision making should balance likely benefits and harms for the individual patient.

**Research:** The authors stated that understanding the mechanism by which lithium decreased suicide risk could improve understanding of the neurobiology of suicide.

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