Lithium treatment and suicide risk in major affective disorders: update and new findings

Baldessarini R J, Tondo L, Hennen J

CRD summary
This poorly reported review assessed suicidal risk reduction with long-term lithium maintenance. The authors' concluded that long-term maintenance with lithium is associated with major reductions in risks of suicides and attempts in bipolar I disorder and other recurrent major affective illnesses. The review has several methodological weaknesses. The results from included studies and their subsequent synthesis may not be reliable.

Authors' objectives
To update and extend analyses of published data pertaining to suicidal behaviour in patients treated with and without lithium therapy (see Other Publications of Related Interest nos.1-3).

Searching
MEDLINE (from 1970 to mid-2002) was searched using the keywords 'lithium' and 'suicide'. In addition, the bibliographies of recently published reports were reviewed.

Study selection
Study designs of evaluations included in the review
The authors did not specify any a priori inclusion criteria relating to the study design.

Specific interventions included in the review
Studies of participants treated with, or with and without lithium were eligible for inclusion. For those receiving lithium treatment, maintenance averaged at 3.36 years. For those not receiving lithium treatment, the average follow-up was 5.88 years.

Participants included in the review
Studies of participants with suicidal behaviour were eligible. The diagnoses of the patients in the included studies were major affective disorders, bipolar disorders, or unipolar depression.

Outcomes assessed in the review
Studies reporting the number of suicidal acts (completed and attempts) and persons at risk, as well as the average times at risk, were eligible for inclusion.

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. The rates (events/100 person-years) for each study were calculated.

Methods of synthesis
How were the studies combined?
Rates and risk ratios (RR), along with 95% confidence intervals (CIs), were calculated using random-effects Poisson
How were differences between studies investigated?
Sub-group analyses were carried out for bipolar disorder and major affective disorder. A formal statistical test of heterogeneity was not reported.

**Results of the review**
Thirty-four studies (n=16,221) with 67 treatment arms or conditions (42 with and 25 without lithium treatment) were included. Three of the studies were double-blind randomised controlled trials. The study design of the other 31 studies was not indicated.

Overall. The estimated rate for completed suicides was 0.174 (95% CI: 0.138, 0.215) with lithium treatment versus 0.942 (95% CI: 0.743, 1.180) without; the RR was 5.43 (95% CI: 3.57, 8.25); the reduction was 81.5%. The estimated rates for suicide attempts were 0.312 (95% CI: 0.204, 0.451) and 4.646 (95% CI: 4.104, 5.239) with and without lithium treatment, respectively; the RR was 14.9 (95% CI: 8.41, 26.4); the reduction was 93.3%. The estimated rates for all suicidal acts (completed suicides and suicide attempts) were 0.210 (95% CI: 0.172, 0.253) and 3.100 (95% CI: 2.803, 3.422) with and without lithium treatment, respectively; the RR was 14.8 (95% CI: 8.54, 25.6); the reduction was 93.2%.

Bipolar disorder. The estimated rate for all suicidal acts was 0.295 (95% CI: 0.216, 0.394) with lithium treatment versus 6.102 (95% CI: 5.320, 6.966) without; the RR was 20.7 (95% CI: 11.9, 35.8); the reduction was 95.2%.

Major affective disorder. The estimated rate for all suicidal acts was 0.193 (95% CI: 0.151, 0.244) with lithium treatment versus 2.119 (95% CI: 1.829, 2.441) without; the RR was 11.0 (95% CI: 5.37, 22.4); the reduction was 90.9%.

Further results of comparisons of suicide rates found with and without lithium to general population rates were also presented, as were secular trends in suicide rates and effects of lithium treatment.

**Authors' conclusions**
Long-term maintenance treatment with lithium salts is associated with major reductions in risks of suicides and attempts in bipolar I disorder and other recurrent major affective illnesses (bipolar II disorder and unipolar depressive) that mainly involve depression.

**CRD commentary**
The review question was clearly stated. However, a priori inclusion criteria relating to the study design were not specified and there was insufficient information about the design of the studies included. The search was restricted to one database, supplemented only by a review of reference lists of recent reports, and the review appears to have been limited to English language publications. Therefore, relevant studies may have been missed, and language and publication bias may be present. The validity of the included studies was not assessed. Hence, the results from these studies, and their subsequent synthesis, may not be reliable. There was no information on how the studies were assessed for inclusion or how the data were extracted from them. Thus, it is not possible to assess whether steps were taken to minimise error and bias in the review process. It is also unclear whether the statistical pooling of the studies was appropriate, as heterogeneity was not formally assessed. The most tentative interpretation of the authors' conclusions is advisable.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice. Research: The authors stated that it is important to include assessments of mortality risk and suicidal behaviour in long-term studies of the effectiveness of anticonvulsants and other alternatives to lithium to treat bipolar disorder. It should also be clarified whether modern antidepressants reduce suicidal risk in recurrent unipolar major depressive illnesses. In addition, further study into the potential
adjunctive role of lithium, or other mood-stabilising agents, as a means of reducing the risk of suicide in recurrent unipolar depression is required.

**Funding**
GlaxoSmithKline.

**Bibliographic details**

**PubMedID**
12720484

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Bipolar Disorder /drug therapy /prevention & control /psychology; Depressive Disorder /prevention & control /psychology; Humans; Lithium /therapeutic use; Mood Disorders /drug therapy /prevention & control /psychology; Risk Factors; Suicide /prevention & control /statistics & numerical data; Suicide, Attempted /prevention & control /statistics & numerical data

**AccessionNumber**
12003001082

**Date bibliographic record published**
30/11/2004

**Date abstract record published**
30/11/2004

**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.