Lower suicide risk with long-term lithium treatment in major affective illness: a meta-analysis
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Authors' objectives
To compare suicide rates with versus without long-term lithium treatment in major affective disorders.

Searching
An open-ended search of Current Contents, MEDLINE, PsycLIT and PubMed was performed; no search terms or dates were reported. The authors also cross-referenced the results with publications on the topic dating from 1949 to December 2000. In addition, the indices and contents tables of leading international psychiatric research journals for the year 2000 were searched. Colleagues who had conducted studies of lithium treatment were contacted for unpublished data. The authors did not state whether any language restrictions were applied.

Study selection
Study designs of evaluations included in the review
The authors stated that all blind or open, controlled or uncontrolled studies were included.

Specific interventions included in the review
Studies of lithium treatment were evaluated. No further details of the intervention were provided.

Participants included in the review
Patients who had been diagnosed with bipolar manic-depressive disorder, or bipolar patients with major affective disorder or schizoaffective disorder, were included in the review. Most of the patients had bipolar disorder, but some studies of major affective disorders may have included some patients with unipolar major depression while a few included schizoaffectives.

Outcomes assessed in the review
Only studies that provided data on completed suicides were included in the review. Studies which lacked data pertaining to suicides, or which only included suicide attempts, were excluded.

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
Studies were assessed for quality on the basis of the following criteria: the presence of patients observed both with and without lithium treatment (1 point); randomised treatment assignment and blind clinical assessments (1 or 2 points); more than 100 patients per treatment group (1 or 2 points); and duration more than one year per treatment group (1 or 2 points). The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
Fatality rates due to suicide during maintenance lithium treatment were compared with rates after the discontinuation of lithium or in untreated samples. Study-specific rates were estimated for on- and off-lithium groups in each study. The confidence intervals (95% CIs) of these rates were estimated using Poisson-modelling methods for study groups with non-zero suicide rates and exact estimation methods (also Poisson-based) for studies with zero rates.

A study that found no suicides in either treatment group was excluded from the analysis. Eight studies examined the outcomes after lithium discontinuation, and thus have the potential for treatment discontinuation effects. For these studies, the suicide risk ratios were estimated using survival analysis methods.

The mid-point of time-on-lithium and half of the exposure-time without lithium were taken as the best estimates of time to suicide for on- and off-lithium conditions in the other studies. Time-at-risk for non-suicidal patients was assumed to be the entire exposure time during lithium treatment.

The methods of DerSimonian and Laird were used to combine the risk-ratios obtained for all 12 studies providing non-zero suicide rates with or without lithium treatment. The use of fixed-effect or random-effects models to estimate pooled suicide risk ratios depended upon the size of the Q-statistic.

Publication bias was assessed using a funnel-plot.

How were differences between studies investigated?
Heterogeneity was assessed using the Q-statistic. The presence of studies unduly influencing statistical modelling was assessed by omitting one study at a time from the estimation procedure; the outlier status was verified by Q-tests. Sensitivity analyses, substituting other interval percentiles for the exposure mid-point, were performed to assess the impact of using interval mid-points in estimating the time-at-risk for suicidal patients. Bivariate analyses were used to correlate study treatment group-specific suicide rates with study size, year of publication, diagnostic categories, use of blinded versus open study designs, the presence of lithium discontinuation as a potential risk factor, the presence of one or two treatment conditions, and the overall ratings of study quality. These were carried out for all studies, based on Spearman rank correlations and random-effects regression modelling. Random-effects meta-regression methods were used in 12 studies with on- and off-lithium subgroups.

Results of the review
Twenty-two studies with a total of 5,647 participants were included. Only 3 studies were blinded randomised controlled trials.

The aggregate suicide rate, based on a weighted random-effects model, was 0.159%/year (95% CI: 0.133, 0.204) during lithium treatment and 0.875%/year (95% CI: 0.630, 1.119) off-lithium. This indicated an overall 5.50-fold lower crude suicide risk associated with lithium treatment.

Twelve studies, which included patients with and without lithium treatment and non-zero suicide rates without treatment, yielded overall suicide rates of 1.02%/year (95% CI: 0.80, 1.29) without treatment versus 0.15%/year (95% CI: 0.10, 0.23) with lithium treatment, a significant crude difference of nearly 7-fold (P<0.001). However, there was significant heterogeneity (Q=23.4, P=0.016). Therefore, the random-effects model was used to estimate the log risk ratio for the on- versus off-lithium contrast. The pooled log rate ratio was 2.18 (95% CI: 1.42, 2.95), indicating a risk ratio of 8.85 (95% CI: 4.14, 19.1), which was highly significantly different from the null risk ratio of 1.0 (P<0.0001). The removal of any single study did not significantly affect the pooled risk ratio estimate.

Bivariate analyses of suicide rates found no significant relationships between suicide rates, either with or without lithium treatment, and the number of participants in the study, study quality score, blind study design, discontinuation of lithium, diagnoses, exposure time or publication year. These conclusions were sustained in multivariate logistic regression analyses.

The off-lithium suicide rates did not differ significantly between the 8 studies that involved treatment discontinuation (1.009%/year, 95% CI: 0.754, 1.323) and the 5 studies that did not (1.052%/year, 95% CI: 0.660, 1.593) (P=0.91). This comparison, and the higher suicide rate in studies that involved observations only in lithium-treated patients, suggested that it was unlikely that lithium-treated patients had a lower suicide risk independent of treatment, or that...
treatment discontinuation accounted for the higher suicide risk without lithium.

The quality ratings of the studies averaged 46.8% (range: 14.3 to 100). Publication bias was assessed using a funnel plot and was non significant (t=2.08, P=0.082).

Authors’ conclusions
Suicide risk was consistently lower during long-term treatment of major affective illnesses with lithium in all studies in the meta-analysis, including the few involving treatment randomisation.

CRD commentary
The review question was well-defined and the inclusion criteria were appropriate. The search strategy was adequate, although the search terms and dates were not reported and the authors did not state whether any language restrictions were applied. Publication bias was assessed and was not found to be present. The authors did not state how the papers were selected for the review, or how the quality assessment and data extraction processes were performed. Therefore, there may have been the opportunity for the introduction of bias or errors. The quality of the studies was systematically assessed using appropriate quality criteria. The included studies were described in sufficient detail and the data synthesis appears to have been appropriate. Heterogeneity was assessed and sensitivity analyses were performed.

With the exception of the lack of detail on the review methodology, the review appears to have been generally well conducted and the authors’ conclusions seem appropriate.

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

Research: The authors stated that well-designed, long-term studies comparing randomly assigned, clinically and ethically plausible alternative treatment options, to assess their effects on suicide risk and other forms of mortality in bipolar disorder, continue to be needed.

Bibliographic details

PubMedID
11531653

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Bipolar Disorder /drug therapy; Female; Humans; Lithium /therapeutic use; Male; Middle Aged; Multivariate Analysis; Odds Ratio; Retrospective Studies; Suicide /prevention & control; Time Factors

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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.