Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials

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CRD summary

This review evaluated the efficacy and acceptability of lithium for relapse prevention in bipolar disorder. It concluded that lithium reduces the risk of relapse in bipolar disorder, and that the preventive effect is clear for manic episodes but not for depressive episodes. Given some uncertainty in the review methodology, the validity of the authors' conclusions is unclear.

Authors' objectives

To determine the efficacy and acceptability of lithium for relapse prevention in bipolar disorder.

Searching

The Cochrane Controlled Trials Register and the Cochrane Depression, Anxiety and Neurosis Group's Controlled Trials Register were searched. Two journals (Lithium and Lithium Therapy Monographs) were handsearched, as were abstracts from the Third International Conference on Bipolar Disorders. The reference lists of trials, textbooks and other publications were checked, and trial authors, experts and pharmaceutical companies were contacted.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) with a minimum of 3 months' follow-up were eligible for inclusion.

Specific interventions included in the review

Studies of lithium compared with placebo were eligible for inclusion. Studies evaluating other interventions were included, but only the results of patients in the lithium and placebo arms of the trial were utilised. The levels of lithium used in the included studies ranged from 0.5 to 1.4 mmol/L.

Participants included in the review

Studies of patients with bipolar disorder were eligible for inclusion. Studies of patients who were stable on long-term lithium regimens and were then randomly assigned to continue or abruptly discontinue the drug were excluded. Studies reporting results for mixed groups of bipolar and unipolar patients were also excluded. The participants in the included studies were diagnosed with either manic depressive disorder, or bipolar I or II disorder. Previous use of lithium varied across the studies.

Outcomes assessed in the review

The primary outcomes were any relapse (as defined in the primary study), manic relapse and depressive relapse. The secondary outcomes were withdrawal from the study as an indicator of acceptability, and adverse events. The definition of relapse varied between the studies.

How were decisions on the relevance of primary studies made?

The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality

Study quality was assessed in relation to randomisation, allocation concealment, blinding and handling of withdrawals. 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. The relapse rate for lithium and placebo was extracted, and a risk ratio with 95% confidence intervals (CIs) was calculated for each study. Intention-to-treat data were used where possible; alternatively, end point data for trial completers were used.

Methods of synthesis

How were the studies combined?

Pooled risk ratios and 95% CIs were calculated using a fixed-effect model. Where heterogeneity was observed and appeared quantitative (all trials finding the same direction of treatment effect), a random-effects model was used. When the heterogeneity appeared to be qualitative (material differences in the direction of the treatment effect between trials), the data were not pooled. The number-needed-to-treat (NNT) was also calculated.

How were differences between studies investigated?

Heterogeneity was assessed using the chi-squared statistic. The authors stated that they investigated potential sources of heterogeneity when it was detected, but did not report the method used. Forest plots were presented to enable a visual inspection of heterogeneity.

Results of the review

Five RCTs (n=770) were included in the review.

Quality.

Concealment of allocation was unclear in all 5 RCTs. The blinding of patients and outcome assessors was reported in 3 RCTs, with clinicians also blinded in two of these.

Relapse.

Lithium showed a statistically significant benefit over placebo for preventing new episodes of mood disturbance, with the average risk of relapse being 40% and 60%, respectively. The overall random-effects relative risk (RR) was 0.65 (95% CI: 0.50, 0.84, P=0.001; 5 RCTs) and the NNT was 5. There was statistically significant heterogeneity between studies (P=0.04).

Lithium showed a statistically significant benefit over placebo for preventing manic episodes, with the average risk of a manic episode being 14% and 24%, respectively. The overall fixed-effect RR was 0.62 (95% CI: 0.43, 0.88, P=0.008; 4 RCTs) and the NNT was 10. There was no statistically significant heterogeneity between studies (P=0.27).

Lithium showed no statistically significant benefit over placebo for preventing depressive episodes, with the average risk of a depressive episode being 25% and 32%, respectively. The overall fixed-effect RR was 0.78 (95% CI: 0.60, 1.01, P=0.06; 4 RCTs) and the NNT was 14. There was no statistically significant heterogeneity between studies (P=0.20).

Acceptance.

There were statistically significantly fewer withdrawals in patients taking lithium compared with those taking placebo; the fixed-effect RR was 0.86 (95% CI: 0.80, 0.93).

Adverse events.

There was statistically significantly more cases of somnolence (RR 1.98, 95% CI: 1.02, 3.84), nausea (RR 1.76, 95% CI: 1.07, 2.92) and diarrhoea (RR 2.35, 95% CI: 1.35, 4.10) with lithium compared with placebo. The results of the statistical test for heterogeneity were not reported, and it was unclear whether the results were from a fixed-effect or random-effects meta-analysis. There was no significant difference in the occurrence of hypothyroidism or suicide between groups.

Authors' conclusions

Lithium reduces the risk of relapse in bipolar disorder. The preventive effect is clear for manic episodes but not for depressive episodes.

CRD commentary

The review question was clear in terms of the participants, intervention, outcome and study design. Although relevant sources were searched, none of the major, general medical bibliographic databases were searched. It was unclear whether language restrictions were applied, and publication bias was not investigated. A lack of information on the methods used to select studies, assess their quality and extract the data makes it difficult to determine whether attempts were made to reduce error and bias during the review process. Study quality was assessed, but only the results for allocation concealment and blinding were reported for each study.

The decision to pool the results for the primary outcome might not have been appropriate, given the clinical heterogeneity between studies in relation to the definition of relapse. The results of both the fixed-effect and random-effects meta-analyses were reported for the main outcome, regardless of the results of the statistical test for heterogeneity. The authors' conclusions appear to be in line with the evidence they present. However, given the uncertainty in the review methodology and some aspects of study quality, the validity of the authors' conclusions is unclear.

Implications of the review for practice and research

Practice: The authors stated that the use of long-term lithium treatment to prevent relapse in patients with bipolar disorder, particularly those suffering mainly from mania, is supported.

Research: The authors stated that the inclusion of a lithium arm in future trials of new agents may inform the estimate of the effect against depressive relapse.

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