Lithium: still a cornerstone in the long-term treatment in bipolar disorder?

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CRD summary
This review assessed the evidence from randomised controlled trials of long-term effects and effectiveness of lithium treatment for bipolar disorder. It concluded that data supports the effectiveness of lithium as a prophylactic agent against mania, but not so much against bipolar depression. Due to limited synthesis and lack of study quality reporting, the results should be interpreted with caution.

Authors' objectives
To review the evidence from randomised controlled trials concerning the long-term effects and effectiveness of lithium treatment for bipolar disorder.

Searching
The authors searched MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) for relevant studies published in English between January 2000 and January 2009. Search terms were reported. Relevant studies and systematic reviews were searched for further relevant studies; systematic reviews were used to locate studies published before 2000. ClinicalTrials.gov and Clinical Study Results were searched.

Study selection
Eligible studies were randomised controlled trials (RCTs) that assessed the effectiveness and/or tolerability of lithium used as a maintenance therapy for bipolar disorder. Studies required at least six months follow-up. Studies of both unipolar and bipolar patients were included only where data for patients with bipolar disorder could be extracted. The primary outcome was time to mood episode; secondary outcomes included manic and depressive relapse rates and change from baseline in rating scale scores.

Some of the included studies were multicentre. Some studies were placebo-controlled. Duration of the blinded phase of the studies ranged from 12 months to 20 months; duration of the subsequent open-label phase ranged from eight weeks to 20 weeks. Comparators included divalproex, lamotrigine and olanzapine. The definition of relapse varied across the included studies. Within included trials, lithium was used as a monotherapy only and generally as comparator drug to a newer drug. The population included both adults and children. Patients with Bipolar I and Bipolar II disorder were included. Some trials were industry sponsored.

The number of reviewers who performed study selection was not reported.

Assessment of study quality
The review states that a quality assessment was performed, but no details were reported. One reviewer performed the quality assessment and a second checked the assessment.

Data extraction
One reviewer performed data extraction; a second reviewer checked the extraction.

Methods of synthesis
A narrative synthesis was performed.

Results of the review
Six trials were considered in the review (n=1,561, range 60 to 463).

The reviewers reported that one study indicated lithium was superior to placebo in preventing mania and hypomania in recently manic or hypomanic patients. Another study indicated lithium was superior to placebo in preventing mania and hypomania in depressed bipolar I patients. One study indicated that lithium was not statistically different to divalproex in terms of mood disorder symptoms. Two studies were interpreted as not demonstrating that divalproex was superior to
lithium. One study indicated that lithium and LMT did not differ in efficacy in preventing mood episodes and that olanzapine was superior to lithium in preventing recurrence of manic and mixed episodes. Summaries of individual studies were reported.

The authors stated that lithium was associated with higher rates of nausea, diarrhoea, tremor and somnolence than placebo. Other comparisons were reported.

**Authors' conclusions**
Data supported the effectiveness of lithium as a prophylactic agent against mania, but not so much against bipolar depression.

**CRD commentary**
This review addressed a clear review question using clearly defined study selection criteria. More than one database and reference lists and other sources were searched, which reduced the risk of publication bias. Not all stages of the review process were reported as conducted by more than one reviewer, so reviewer error and bias could not be ruled out. Study quality was stated as assessed, but was not reported and this reduced review transparency. The extent of synthesis within the pooled results was limited, as most studies were summarised individually. The limited synthesis and lack of reported study quality mean that the results should be interpreted with caution.

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

**Research:** The authors stated that further well-designed trials to ascertain the current role of lithium as a prophylactic agent in manic-depressive illness and its anti-suicidal profile should be conducted.

**Practice:** The authors stated that lithium had a very relevant role for preventing relapses and recurrences in patients with bipolar disorder and its declining use may not be for evidence-based reasons.

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