Lithium toxicity profile: a systematic review and meta-analysis
McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR

CRD summary
This review explored harmful effects of lithium in patients with mood disorders. The authors concluded that increased risks of reduced urinary concentrating ability, hypothyroidism, hyperparathyroidism and weight gain were possible without significant impact on renal function. Potential error and bias in the review process and concerns about the quality and synthesis of studies mean that this conclusion might not be reliable.

Authors' objectives
To assess the evidence for potentially harmful effects of lithium in patients with mood disorders.

Searching
MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, CINAHL, PsycINFO, The Cochrane Library, BIOSIS Previews and TOXNET were searched without language restrictions from inception to 2010. The journals Lithium, Lithium Therapy Monographs and Teratology were searched. References were checked for additional published and unpublished material. Relevant textbooks and conference abstracts were handsearched. Pharmaceutical companies and clinicians were contacted. Full search strategies were reported.

Study selection
Preferentially, controlled studies that compared lithium with placebo, no treatment or other drug therapies in patients with depression or bipolar disorder were included; in the absence of these, studies at lower levels of evidence were included, down to case reports. Studies had to assess one or more of the outcomes: renal function; renal concentrating ability; thyroid function; subclinical hypothyroidism; clinical hypothyroidism; hyperthyroidism; parathyroid function and parathyroid hormone; bodyweight; hair and skin disorders; and teratogenicity. Further descriptive details and parameters for these outcomes were reported in the paper.

A range of study designs was included. Publication dates spanned 1950 to 2010. Studies contained doses and concentrations of lithium that were deemed consistent with current practice, but there was incomplete reporting in some cases. Most studies excluded patients with a history of lithium toxicity; in others it was not possible to separate individuals or link their clinical presentation to toxic events or specific treatment regimens.

Studies were selected by one researcher and those identified for analysis were reviewed by a second researcher.

Assessment of study quality
The quality of randomised controlled trials (RCTs) was assessed on randomisation, allocation concealment, blinding, follow-up, reporting of withdrawals and drop-outs, and method of analysis. For observational studies, measurement bias, treatment of confounders and loss to follow-up were assessed. Authors were contacted for missing details, where necessary.

The authors did not state how many reviewers were involved in the quality assessment.

Data extraction
Data were extracted to enable calculation of mean differences, odds ratios (ORs), relative risks (RRs) and absolute risk differences, all reported with 95% confidence intervals. Authors were contacted for any missing data.

The authors did not state how many reviewers were involved in data extraction.

Methods of synthesis
Odds ratios, relative risks, weighted mean differences (WMDs) or standardised mean differences (SMD) were calculated using fixed-effect (Mantel-Haenszel) and random-effects (DerSimonian and Laird) meta-analyses. Statistical heterogeneity was assessed using X^2 and I^2 and explored with meta-regression analysis. Sensitivity analyses were conducted to explore the effect of excluding poor quality studies and those with discrepant results.
Results of the review
The analysis comprised 385 studies: 22 RCTs; 197 case-control, uncontrolled cohort or cross-sectional studies; and 166 case reports. The authors reported that there was little high-quality evidence. Sample sizes of observational studies and RCTs were generally small. Drop-out rates were high. Follow-up was poorly-defined. Confounding could not be ruled out. Publication bias was a possibility.

Renal function: Thirty studies (nine case-control studies) were included in the quantitative analysis. Lithium therapy resulted in a statistically significant reduction (15% of normal maximum) in urinary concentrating ability (WMD -158.43 milliosmoles (one thousandth of an osmole, mOsm)/kg, 95% CI -229.78 to -87.07 $I^2=81.3\%$; four case control studies) compared to control. There was no statistically significant difference for glomerular filtration rate (six case-control studies). The absolute risk of renal failure was small (0.5% of patients received renal replacement therapy; one study).

Thyroid function: Seventy-seven studies (16 case-control studies) were included in the quantitative analysis. Clinical hypothyroidism increased significantly with lithium therapy compared to control (OR 5.78, 95% CI 2.00 to 16.67, $I^2=52.5\%$; eight studies). Thyroid stimulating hormone increased significantly, on average by 4.00 IU/mL (95% CI 3.90 to 4.10; 16 studies). Thyroid function did not increase significantly (four case-control studies).

Parathyroid function: Sixty studies (four cohort, 14 case-control and six cross-sectional) were included in the quantitative analysis. Statistically significant differences for increased blood calcium were noted for lithium (WMD 0.09mmol/L, 95% CI 0.02 to 0.17, $I^2=99.5\%$; 13 case-control studies) and parathyroid hormone (7.32pg/mL, 95% CI 3.42 to 11.23, $I^2=89.2\%$; 10 case-control studies).

Bodyweight: Fifty-five studies (14 RCTs and 23 cohort studies) were included in the quantitative analysis. Weight gain was significantly greater following lithium therapy compared to placebo (RR 1.89, 95% CI 1.27 to 2.82, $I^2=0\%$; five RCTs) and significantly lower when compared to olanzapine (RR 0.32, 95% CI 0.21 to 0.49, $I^2=0\%$; two RCTs).

Skin disorders: Seventy-seven studies (two RCTs) were included in the quantitative analysis. There was no statistically significant difference in skin disorders between lithium and placebo in a pooled analysis of two RCTs.

None of the studies that assessed hair disorders (24 studies) were included in a quantitative synthesis. There were no significant differences between groups in terms of teratogenic potential (risk of congenital malformations).

Results of meta-regression and sensitivity analyses were not reported.

Authors' conclusions
Lithium was associated with an increased risk of reduced urinary concentrating ability, hypothyroidism, hyperparathyroidism and weight gain. There was little evidence for a clinically significant reduction in renal function. The risk of end-stage renal failure was low. The risk of congenital malformations was uncertain.

CRD commentary
The review question was clear. Inclusion criteria were broad for study design, but potentially reproducible for all aspects. A wide range of data sources was accessed. Attempts were made to minimise publication and language biases. Quality assessment criteria were appropriate to the wide range of included study designs, but results of this were reported only in broad terms and this limited an accurate interpretation of study reliability. The study selection process was conducted with some attempts to minimise error and bias, but was not ideal; the extent to which this applied to other aspects of the review process was unclear.

Study details were sparse in terms of patient characteristics and intervention doses (the latter acknowledged by the authors). There was a discrepancy between graphical presentation and text for thyroid function. High statistical heterogeneity in some of the analyses called into question whether statistical pooling was appropriate.

The authors' conclusion reflects the evidence presented, but relied largely on only a subset of eligible studies. Together with the methodological limitations identified, this suggests that the reliability of this review is uncertain.

Implications of the review for practice and research
Practice: The authors stated that the risks of adverse events of lithium should be discussed with the patient prior to therapy. Serum calcium concentrations should be checked before and during treatment. The balance of risks should be taken into account before lithium withdrawal during pregnancy. Renal, parathyroid and thyroid function should be assessed minimally every 12 months. Blood tests should be repeated in the event of a change in mood state. Adverse events should be recorded as routine practice.

Research: The authors stated a need for further research to explore the relationship between lithium, calcium and renal function.

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