Is the safety of lithium no longer in the balance?

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Ultimately, all therapeutic decisions involve balancing the potential clinical benefits of a drug against the risks that it might confer. In the management of bipolar disorder, trial data[1] which have re-established the efficacy of lithium in prophylaxis have refocused attention on understanding its tolerability profile. Clinical interest in lithium has further heightened because the substantial risks that ensue from the metabolic syndrome have become apparent with newer alternatives, particularly atypical antipsychotics such as olanzapine.[2] Hence, the importance of correctly judging the treatment options for bipolar disorder has never been more crucial.

The use of lithium in the treatment of bipolar disorder has decreased substantially, partly because of active marketing of alternatives, and also because of the perceived risks associated with its use, particularly the effects on renal and endocrine function and the possibility of teratogenicity.[3] In *The Lancet*, Rebecca McKnight and colleagues[4] have attempted to redress this imbalance and are to be congratulated for the systematic quantification of the potential risks that lithium incurs. Their detailed review and analyses provide meaningful advice for clinicians and identify aspects that warrant further investigation. The study adopted a pragmatic hierarchical approach to assessment of the data, and analyses the findings of nearly 400 articles, almost all of which were not randomised controlled trials. Consequently, there are several important caveats that need to be considered in the interpretation of these findings. First, in addition to the fact that most studies were methodologically weak, the different design of studies over six decades of research made the combination of data, and its synthesis, difficult. Second, the absence of key information, such as timing of onset of side-effects in relation to the start of lithium and the concentrations of lithium in plasma attained with various dose regimens, restricts the clinical inferences that can be made. Thus the evidence is far from ideal, but despite these limitations the investigators manage to identify five key areas in which lithium therapy produces adverse effects—namely renal, thyroid, and parathyroid function; teratogenicity; and weight gain.

The renal side-effects of lithium are of greatest concern to both clinicians and patients,[5] and in this regard the analysis is reassuring in that, even with long-term lithium use, the risk of renal toxicity, specifically end-stage renal failure, is fairly low (0·53% compared to 0·2% in the general population).[6] By comparison, chronic kidney disease is more common, but occurs predominantly with increasing age, and only a small proportion of this group (2%) progress to end-stage renal failure. Clinically, polyuria is more troublesome, because it restricts tolerability and reduces drug adherence, but this effect is usually reversible.

Analysis of the data confirms that lithium is associated with modest weight gain, probably similar to that with most alternative drugs, but less than that caused by olanzapine, and the risk of hypothyroidism is significant. Perhaps the most interesting finding is the high prevalence of hyperparathyroidism, reinforcing recommendations for routine monitoring of plasma calcium concentrations.[7] In retrospect, this finding is consistent with lithium's ability to modulate intracellular calcium, the dysregulation of which is a documented pathophysiological finding in bipolar disorder.[8] Notably,

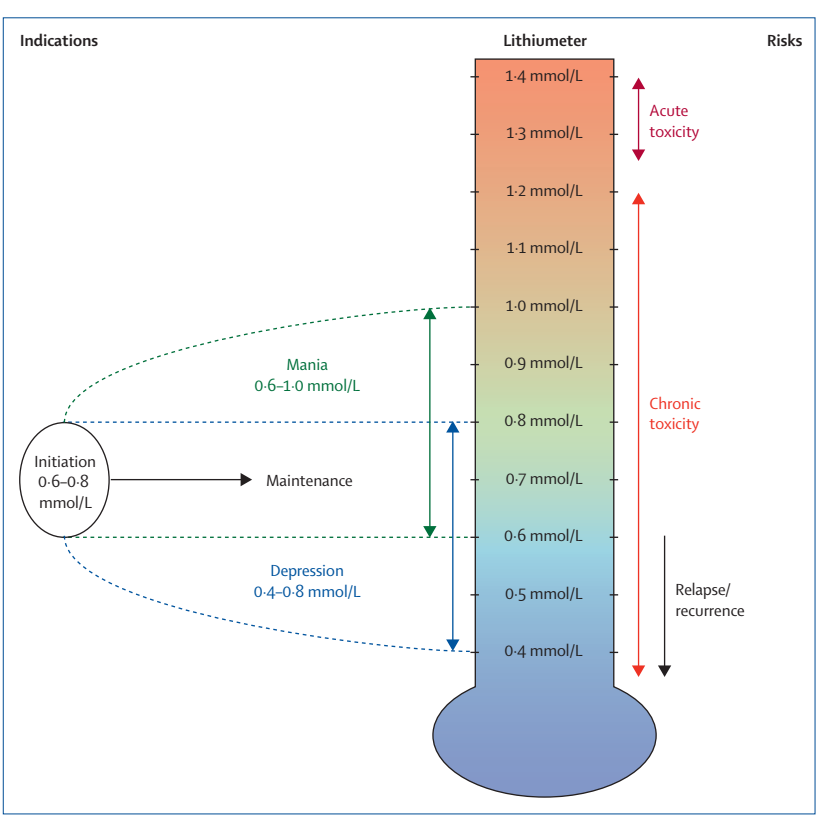

Figure: **The lithiumeter**
Figure depicts the optimum lithium plasma concentrations for the treatment of bipolar disorder and those associated with the risks of toxicity and relapse. Adapted from Malhi and colleagues (2011),[11] with permission.

the investigators did not find an overt risk of congenital malformations, nor did they confirm previous reports of alopecia or skin disorders.

In practice, the oral dose of lithium and the plasma concentrations that it routinely achieves are of fundamental importance to ensure both optimum efficacy and adequate tolerability.[9] The therapeutic serum concentrations of lithium are reasonably well defined (0·4–0·8 mmol/L), but the greater efficacy of concentrations greater than 0·6 mmol/L—more necessary for acute mania, and to a lesser extent for its prophylaxis—come[5] at a cost in terms of tolerability,[10] whereas lower plasma concentrations that might provide adequate depression prophylaxis and reduce the risks of long-term toxicity might not optimally reduce the recurrence of mania (figure).[12] Clinically, the dose of lithium can change the likelihood of side-effects—eg, once-daily dosing can maintain therapeutic plasma concentrations and yet keep the risks of long-term toxicity to a minimum.[13] Furthermore, several lithium side-effects are dose dependent, including tremor, diarrhoea, and weight gain,[14] and concentrations indicating incipient intoxication should prompt immediate measurement of plasma concentrations and appropriate dose adjustment. However, because of insufficient data these issues cannot be informed by the findings from McKnight and colleagues' analysis. Instead the study provides useful guidance for clinicians considering lithium treatment, and redirects the focus of research to dosage and safety monitoring.

In the context of efficacy data that have upgraded the ranking of lithium, and in conjunction with new data that recalibrate the safety risks of alternative drugs,[15] this study provides timely clarification of the toxicity associated with lithium therapy and, on balance, reaffirms its role as a treatment of choice for bipolar disorder.

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