

Lithium therapy in bipolar disorder: a balancing act?



Quite reasonably, patients with bipolar disorder want treatment that provides sustained relief from their illness without incurring serious side-effects. Functionally, this translates to the resumption of purpose and enjoyment. But of the numerous drugs available for the management of bipolar disorder, only lithium seems to truly stabilise mood.¹ Its status as an effective prophylactic agent was convincingly reinstated by the findings of the randomised, open-label BALANCE trial,² which corroborated empirical knowledge. The BALANCE investigators showed that lithium alone, or lithium plus valproate, are more likely to prevent relapse than valproate monotherapy, and prophylaxis with lithium monotherapy might be on a par with lithium plus valproate. Hence, despite fluctuating popularity, lithium remains a first-line option for the treatment and prophylaxis of bipolar disorder in therapeutic guidelines.³ However, use of lithium in practice is limited by concerns about safety and adverse effects with long-term use.

Extending previous research that examined the short-term tolerability of lithium,⁴ in *The Lancet* Brian Shine and colleagues⁵ have drawn on a large set of data to determine the long-term effects of lithium on renal and endocrine function. Data from 4678 patients were included in the study, of whom 2795 had their serum lithium measured more than once. Shine and colleagues' findings show that lithium was associated with increased risk of stage three chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73m²; hazard ratio 1.93, 95% CI 1.76–2.12), hypothyroidism (thyrotropin activity >5.5 mU/L; 2.31, 2.05–2.60), and hypercalcaemia (1.43, 1.21–1.69). These findings send a key message to clinicians to monitor lithium therapy closely from the outset. Both thyroid hormone secretion and renal function can decline with long-term lithium use and can, in some cases, lead to hypothyroidism and stage three chronic kidney disease. Interestingly, these complications are more likely to occur in women than in men, and are detected early in the course of lithium treatment. In addition, long-term lithium therapy can also cause hypercalcaemia (ie, total plasma calcium concentration ≥ 2.6 mmol/L). All adverse effects are more likely to occur when plasma lithium concentration is high.

Therefore, patients receiving lithium therapy should have thyroid function, renal clearance, and blood calcium concentrations assessed carefully at the beginning of therapy and monitored closely thereafter. Shine and colleagues⁵ provide clear evidence of the potential risks associated with long-term lithium treatment. But because bipolar disorder typically emerges at a young age⁶ and requires lifelong treatment, these findings prompt the question: how can these hazards be navigated?

The answer is twofold. First, avoid sustained periods during which plasma lithium concentrations are high to diminish the risk of serious adverse effects. Second, all the parameters that need regular assessment, such as thyroid and renal function tests and plasma lithium and calcium concentrations, can be measured reliably and easily. However, the treatment of type I bipolar

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Figure: The Lithium Membrain by Anne Naylor

Lithium coursing through veins in the brain (blue) provides mood stability by acting as a membrane that prevents the effects of the various faces of the illness (circles) on the brain (neural networks).

disorder, the subtype best suited to lithium therapy,⁷ is often complicated by comorbid anxiety and substance misuse. Furthermore, lithium's therapeutic effect occurs at concentrations that can be toxic if maintained in the long term.⁸ These concerns reinforce a widely held view that lithium therapy is problematic. But all drugs are associated with side-effects, and long-term management often involves a risk-benefit analysis at some point in the treatment course; lithium is no exception.

Maintenance of lithium concentrations at the lower end of the therapeutic range (ie, 0.6 mmol/L) can reduce the adverse outcomes associated with lithium treatment. For plasma lithium concentrations to be high enough to be efficacious, but low enough to avoid toxicity, is a delicate balance. The simple pharmacokinetics of lithium in plasma offer some assistance, but the pharmacokinetics of lithium within the brain are more complex because the blood-brain barrier insulates the brain from rapid changes in plasma lithium concentration and facilitates its accumulation in neural tissues, which can be neurotoxic.⁹ The movement of lithium between plasma, cerebrospinal fluid, and brain tissue is not fully understood, and future research will need to examine the effects of different doses and duration of lithium treatment on concentrations within these various compartments. For example, a low concentration of lithium in the plasma (0.2–0.4 mmol/L) has little effect on renal and thyroid function,¹⁰ and is achievable with alternate-day dosing.⁹

Lithium is without doubt the best treatment for many patients with bipolar disorder because it confers long-term mood stability and prophylaxis (figure). Lithium also reduces the risk of suicide¹¹ and is possibly neuroprotective.¹² The dilemma of lithium therapy arises because, if poorly managed, lithium can compromise renal function, sometimes irreversibly, and severely

disrupt endocrine homeostasis—ultimately limiting its usefulness. Therefore, lithium therapy remains a challenge that will benefit from a better understanding of its therapeutic properties.

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