

Graylands Hospital

Drug Bulletin

Using Lithium Safely

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Introduction

It has been over 60 years since Australian psychiatrist John Cade first described lithium's therapeutic role in manic illness¹. Cade's seminal 1949 article described the impact of lithium salts in resolving "psychotic excitement" in 10 manic patients.¹ Since this discovery, lithium has become a gold standard treatment for bipolar disorder, with evidence supporting its role in acute mania,² depression³ and prophylactic treatment.⁴ It is also efficacious as augmentation therapy in refractory unipolar depression.⁵ In addition, it has been noted to effect aggressiveness,⁶ reduce suicide rates in affective disorders⁷ and, more speculatively, has been considered as a possible therapeutic agent for treating chronic neurodegenerative diseases.⁸

Yet, despite lithium's extensive clinical applications and its ability to provide potentially lifesaving treatment, its use has been limited due to concerns regarding tolerability, long-term effects, toxicity and the requirement for regular monitoring of plasma levels. This bulletin presents an overview of the role of lithium in bipolar illness with particular emphasis upon efficacy, tolerability, toxicity and monitoring.

Mechanism of action

Despite being a simple element, lithium affects many complex biological systems, and even after 60-years of use, the exact mechanism of action remains unknown. It's likely to be multifactorial and the following has been postulated: (for a comprehensive review, see Marmol).⁸

- Reduction of intracellular concentrations of sodium and calcium, which may be elevated in patients with bipolar disorder.
- Reduced activity of sodium-dependent intracellular secondary messenger systems.
- Modulation of dopamine and serotonin neurotransmitter pathways.
- Reduced activity of protein kinase C and reduced turnover of arachidonic acid.
- Neuroprotective and neuroregenerative effects, through mediation on N-methyl-D-aspartate (NMDA) pathways.

Efficacy in bipolar disorder

Acute mania

After Cade¹ discovered lithium as a potential drug for acute mania, numerous studies confirmed the antimanic efficacy of lithium. However, these earlier studies had methodological flaws, and it wasn't until 1994 that Bowden *et al*⁹ reaffirmed lithium's effectiveness as an antimanic drug. In this study, which was the first placebo controlled parallel group designed study on lithium in mania, response rates of 49%, 48%, and 25% for lithium, valproate and placebo, respectively, were found over a period of three weeks. For lithium the number needed to treat (NNT) was 5.⁹

If proof were still needed of the efficacy of lithium in mania, then the recent meta-analysis by Storosum provides it. This study found that lithium was effective in the treatment of acute mania, with an overall effect size of 0.40 (95% confidence interval (CI) 0.28- 0.53) and an overall NNT of 6.²

However, the use of lithium in acute mania does have some limitations. It usually takes at least a week to achieve response¹⁰ and it may be less effective for patients with agitation.^{11,12} It can also be difficult to achieve therapeutic plasma levels rapidly and monitoring can be problematic if the patient is uncooperative.

Acute bipolar depression

The evidence for lithium in the treatment of acute bipolar depression is nowhere near as extensive as for acute mania. Its effectiveness in acute bipolar depression stems from a small number of underpowered trials from the early 1970s.¹³ More recently, the EMBOLDEN I trial,¹⁴ which aimed at testing the efficacy of quetiapine against placebo in bipolar depression and lithium was incorporated to ensure the validity of the design, found that lithium did not differ significantly from placebo. However, serum concentrations of lithium were relatively low (mean 0.61 mmol/L). Despite this, lithium is still widely regarded as an important agent for the treatment of acute bipolar depression.¹⁵⁻¹⁷

Prophylaxis of bipolar disorder

The main indication for lithium is in the prophylaxis of bipolar disorder where it reduces both the number and the severity of relapses.¹⁸ Lithium is more effective at preventing manic than depressive relapse.¹⁹ The NNT to prevent relapse into mania or depression has been calculated to be 10 and 14, respectively.¹⁹ Data from the Balance study (Bipolar Affective disorder: Lithium/Anti-Convulsant Evaluation) in 2010 firmly positioned lithium as an effective prophylactic agent in the maintenance treatment of bipolar disorder. The key findings from this study suggested that lithium has superior maintenance efficacy compared to valproate, with the combination showing greatest overall efficacy.²⁰

Efficacy in unipolar depression

Lithium has been used to augment the efficacy of antidepressant medications for more than 30 years. One of the very first studies was performed by de Montigny *et al*²¹ who reported a dramatic response within 48 hours to the addition of lithium in 8 patients who had not responded to tricyclic antidepressants. Since then numerous RCTs and open studies have been conducted on the use of lithium augmentation in refractory depression. A recent meta-analysis found lithium to be three times as effective as placebo for this indication with a NNT of 5.²² More modest results from the STAR-D programme, found remission rates of 15.9% in patients receiving lithium, who had not responded to previous antidepressant treatments.

Unlicensed indications

Lithium increases the neutrophil count & total white cell count (WCC) both acutely and chronically.²³ This 'side-effect' of lithium has been used successfully to raise the WCC in patients who have developed neutropenia with clozapine, thus allowing clozapine treatment to continue. Lithium has also been reported to speed the recovery of the WCC when prescribed after the development of clozapine-induced agranulocytosis.²⁴ A serum lithium level of >0.4mmol/l may be required. Lithium is also used to treat aggressive and self-mutilating behaviour.²⁵

More surprisingly, evidence is developing that lithium may confer benefits in terms of preventing dementia²⁶ and for the treatment of neurodegenerative disorders like Alzheimer's disease.⁸ This is mainly due to in vitro and in vivo studies that have revealed neuroprotective effects of lithium.⁸

Lithium and suicide

It has been repeatedly shown that lithium has a unique antisuicidal effect. This finding is highly significant given that patients with bipolar disorder are approximately 15 times more likely to commit suicide than the general population.²⁷ A meta-analysis of clinical trials from 2006 concluded that lithium reduced by 80% the risk of both attempted and completed suicide in patients with bipolar disorder.²⁸ More recently, Cipriani and colleagues updated meta-analysis, of 6674 participants from 48 randomised trials, found that lithium was better than placebo in reducing suicidal events and overall mortality, and its effect was superior to some mood stabilising and antidepressant drugs.²⁹ The mechanism of this protective effect is unknown.

Plasma levels

For most patients the therapeutic serum lithium concentration for prophylaxis of bipolar disorder is 0.6- 0.8 mmol/L.³⁰ Some patients may need a concentration of 0.8-1.0 mmol/L and some may be maintained satisfactorily at 0.4-0.6 mmol/L.³⁰ Levels above 0.75 mmol/L offer additional protection against manic symptoms.³¹ Recent long-term studies suggest that even relatively low concentrations (0.6-0.75 mmol/L) confer reasonable prophylaxis.³¹ Once steady state is achieved (5-7 days) blood samples should be taken 8-12 hours after the last dose.³⁰

Because of lithium's relatively narrow therapeutic index, pharmacokinetic interactions with other drugs can result in an increase in lithium levels and precipitate lithium toxicity. Interactions of most concern involve Angiotensin Converting Enzyme (ACE) inhibitors, thiazide diuretics and Non-steroidal anti-inflammatory drugs (NSAIDs). Combinations of lithium with any of these drugs can lead to large and often unpredictable increases in lithium levels. Conversely, the use of antacids containing sodium bicarbonate (eg Salvital®, Ural®, Citralite® or Citravescent®) can lead to reduced lithium levels and reduced effectiveness.

Adverse effects

Acute adverse effects

Clinically many patients find lithium difficult to tolerate. Some find virtually no side effects but others will have severe gastrointestinal effects and intolerable thirst/dry mouth and metallic taste. Prescribers need to be prepared to work with patients on the individual experiences of side effects closely. Mild gastrointestinal effects such as nausea, vomiting and diarrhoea (generally transient), tremor, thirst and polyuria are all relatively common side effects observed with the early use of lithium. Fine hand tremor may occur in up to 65% of patients.³² Reducing the use of caffeine can have a positive effect, but

some patients may need treatment with beta-blockers such as propranolol. Lithium inhibits the stimulating effect of antidiuretic hormone on the resorption of water in the collecting ducts of the nephron, resulting in nephrogenic diabetes insipidus. This causes polyuria, dehydration, thirst and compensatory polydipsia. This effect is usually reversible in the short to medium term (< 6 years) but is often irreversible after long-term treatment (>15 years).³³

Longer term adverse effects

Renal effects

Lithium treatment can lead to a reduction in the glomerular filtration rate (GFR), with one large cross-sectional study showing that a third of young people prescribed lithium had an eGFR of <60ml/min (chronic kidney disease stage 3).³⁴ A recent meta-analysis of case-control studies, conducted by McKnight et al,³⁵ demonstrated a reduction in urinary concentrating ability of 15% in lithium-treated patients compared to controls, with a mean observation time of 1 year. A relatively small decline in glomerular filtration rate was also observed (0-5 mL/min over each year of observation). The authors conclude that 'there is little evidence for a clinically significant reduction in renal function in most patients, and the risk of end stage renal failure is low.

The degree of renal impairment may be associated with the serum level. Kirkham and colleagues³⁶ found that a single incident of a lithium level >1.0 mmol/L is associated with a significant decrease in eGFR in the following 3 months when compared to patients whose lithium levels never exceeded 0.8 mmol/L.

Thyroid disorders

In patients treated with lithium, hypothyroidism and goitre are the most prevalent thyroid abnormalities.³⁷ Reported prevalence rates of goitre are 4% to 51% and hypothyroidism is increased about six-fold. In middle-aged women, the risk of hypothyroidism may be up to 20%.³⁸ Goitre is thought to be due to the inhibitory effects of lithium causing increased TSH concentrations. Hypothyroidism is easily treated with thyroxine. Thyroid function test results usually return to normal when lithium is discontinued.

Long-term treatment with lithium also increases the risk of hyperparathyroidism and hypercalcaemia. In one study, patients treated with lithium for more than 15 years were 3-6 times more likely to develop hypercalcaemia than the general population.³⁹ Clinical consequences of chronically increased serum calcium include renal stones, osteoporosis, dyspepsia, hypertension and renal impairment. Calcium levels should therefore be checked annually.

Table 1: Side effects of lithium

Cardiovascular effects <i>Sinus node dysfunction, ECG changes</i>
Cognitive effects <i>Memory impairment</i>
Dermatological effects <i>Psoriasis, acne, dry skin, alopecia</i>
Endocrine/metabolic effects <i>Hypothyroidism, hyperthyroidism, hypercalcaemia, weight gain</i>
Gastrointestinal effects <i>Nausea, diarrhoea, dry mouth, metallic taste</i>
Haematological effects <i>leucocytosis</i>
Nervous system effects <i>Tremor, fatigue, muscle weakness</i>
Renal and Urinary effects <i>Polyuria, polydipsia, nephrogenic diabetes insipidus, renal impairment</i>
Miscellaneous effects <i>Peripheral oedema</i>

Others side effects

Psoriasis, acne, folliculitis and maculopapular eruption have been described as adverse reactions to lithium.⁴⁰ Alopecia (hair loss) is also prevalent occurring in 12-19% of patients receiving long-term therapy.⁴¹ The hair loss is reversible in most cases upon dose reduction or cessation of lithium. A small proportion (9%) of hair loss might result from thyroid dysfunction induced by lithium.⁴⁰ Weight gain is seen in about a third of patients on lithium, is more common in woman, and is an important cause of noncompliance.

Lithium toxicity

Toxicity reliably occurs when the serum lithium concentration is > 1.5 mmol/L, although it can sometimes develop when the level is within the therapeutic range. A patient's lithium concentration may increase, for example, because of co-prescription of a drug which reduces lithium excretion (most commonly an NSAID or thiazide diuretic) or because of simple dehydration. Risk factors for toxicity when serum lithium levels are in the therapeutic range include a high starting dose, concomitant antipsychotic drug therapy, pre-existing EEG abnormalities, undetected cerebral pathology and genetic susceptibility.⁴²

Box 1: features of lithium toxicity

Gastrointestinal effects - <i>anorexia, nausea, diarrhoea</i> Central nervous system effects - <i>increasing malaise & loss of executive functions/confusion, muscle weakness, drowsiness, ataxia, coarse tremor, muscle twitching: >2 mmol/l - disorientation, seizures, coma and death</i>
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Monitoring lithium⁴³

Baseline tests

Before prescribing lithium, renal (eGFR), thyroid (TFTs), weight and cardiac function should be checked. An ECG is recommended in patients who have risk factors for, or have existing cardiovascular disease.

On-going monitoring

Lithium levels should be checked every 3 to 6 months and eGFR and TFTs should be checked every 6 months. More frequent tests may be required in those who are prescribed interacting drugs. Weight (or BMI) should also be monitored (see table 2).

Despite the existence of explicit standards for monitoring patients prescribed lithium, audits consistently show that monitoring is suboptimal. One large audit from the UK, conducted by the Prescribing Observatory for Mental Health (POMH-UK),⁴⁴ found that one in 10 patients prescribed long-term lithium had no documented lithium blood level, one in five patients had no renal function tests documented and one in six patients had no TFTs documented.

A patient safety alert related to this has been issued by the National Patient Safety Agency.⁴⁵

For more information see:

www.nrls.npsa.nhs.uk/resources/type/alerts

Table 2: Recommendations for monitoring patients on lithium³⁰

Test	Frequency
Lithium plasma level	3-6 months
Renal function (eGFR)	Baseline then every 3-6 months
Thyroid function (TFTs)	Baseline then every 6-12 months
Calcium	Baseline then annually
Weight	Baseline then annually

Stopping lithium

It may be prudent to avoid lithium therapy in patients with poor compliance, as intermittent use of lithium may worsen the natural course of bipolar illness.²³ If lithium is to be discontinued then it should be done very gradually to minimise the high risk of manic relapse. The risk of relapse may be reduced by decreasing the dose gradually over a period of at least four weeks, and avoiding decremental serum level reductions of >0.2 mmol/L.³¹

Informing the Patient

At the start of lithium therapy and throughout their treatment, patients should receive appropriate verbal

and written information. This information should cover the following:

Box 2: Key information for Patients

- Information about likely side-effects and how to manage them should they occur
- The importance of regular serum plasma levels and the dangers of lithium toxicity. This should include a description of the key features of lithium toxicity and how it may be prevented
- Patients should be warned not to take over-the-counter NSAID's
- Ensure they maintain their fluid intake, particularly after sweating (for example, after exercise, in hot climates, or if they have a fever)
- Seek medical attention if they develop diarrhoea and/or vomiting
- Importance and significance of regular on-going monitoring of kidneys and thyroid.
- Erratic compliance or rapid discontinuation may increase the risk of manic relapse
- Talk to their doctor as soon as possible if they become pregnant or are planning a pregnancy.

Conclusion

Despite over 60 years of use, and the proliferation of a number of heavily marketed alternative compounds, lithium still remains a key treatment for bipolar disorder. Lithium is effective in alleviating the symptoms of both acute mania and depression, and confers mood stability in the longer term. In addition, lithium possesses unique additional qualities, in particular its neuroprotective, neurotrophic and antisuicidal actions. However, lithium does need to be carefully monitored and clinicians should ensure that patients are fully informed about the risks of toxicity and adverse effects. Lithium management is not easy and many patients will cease lithium early unless we work closely with them. It is essential therefore that all healthprofessionals are well acquainted with the basic principles of lithium treatment.

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