ARTICLE

Safe and effective use of lithium

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SUMMARY

Lithium has proven efficacy in the treatment of bipolar disorder, both for acute mania and long-term mood stabilisation and prophylaxis.

It is also useful in combating treatment-resistant depression.

Compared to other mood stabilisers, lithium has a favourable efficacy–tolerability balance.

Lithium is underused due to active marketing of alternatives and concerns regarding adverse effects, tolerability, and the perception that regular monitoring is difficult.

Introduction

Lithium has been available for over sixty years for bipolar disorder. A large empirical evidence base has ensured it remains a viable treatment option, even in the absence of sponsorship and promotion.[1-3]

Lithium has unique properties both as an antisuicidal and neuroprotective drug and, if used wisely, is relatively well tolerated and not complex to administer. Despite this, its role as a mood stabiliser in practice has been limited because of concerns regarding tolerability and long-term risks, and the perception that regular and reliable monitoring of plasma concentrations is difficult.

Efficacy in bipolar disorder

Lithium is particularly effective in patients with recurrent bipolar I disorder in which episodes of depression and mania are punctuated by periods of remission (euthymia). Complex forms of bipolar disorder such as bipolar II disorder, mixed states, and rapid cycling are common, but respond less well to lithium (Table 1).

In recent years the reported response to lithium in bipolar disorder has diminished. This is partly because studies investigating new treatments, in which lithium has often served as a comparator, have increasingly used heterogeneous bipolar populations.[4] The patients usually have mixtures of bipolar disorder 'subtypes' from bipolar I disorder to major depression. Studies in first world countries often enrol individuals who have been refractory to pharmacotherapy, so not surprisingly the efficacy of lithium appears lower than expected.

A recent real-world study comparing lithium and valproate alone and in combination reaffirmed lithium as an effective first-line drug for maintenance therapy and perhaps the best drug for prophylaxis.[5] Recent guidelines state that in addition to its clear prophylactic properties, lithium is also efficacious in the acute phases of bipolar disorder (Table 1).[6]

Mania

Robust randomised controlled data from trials indicate that lithium is effective in treating acute mania. However, its relatively slow onset of action (6–10 days) means it is used in combination with short-term antipsychotics and benzodiazepines.[1]

Depression

The evidence for lithium monotherapy in the treatment of bipolar depression is not as impressive as that for mania, partly because it can take 6–8 weeks to take effect. Recent clinical trials suggest that lithium is more effective than placebo and therefore it remains an important option for treating bipolar depression.[7]

Maintenance and prophylaxis

The efficacy of lithium in prophylaxis has been robustly demonstrated by the BALANCE study.[5] With adequate adherence, long-term lithium successfully reduces suicidal ideation.[1] Consistency of treatment is therefore important and commencing maintenance therapy early provides the best possibility of improved long-term outcomes.[3] Furthermore, long-term therapy may confer neuroprotection by enhancing the viability of cells as well as preventing apoptosis.

Rapid cycling bipolar disorder and mixed states

Clinically, rapid cycling bipolar disorder and mixed states can often be difficult to differentiate[1] and in practice lithium is relatively less effective in achieving remission in both of these subtypes compared to bipolar I disorder. However, it does reduce symptom severity and can therefore be used combined with other psychotropic medications, especially when wanting to reduce the risk of suicide and achieve prophylaxis.

Starting lithium therapy

Lithium is available in a variety of formulations. The sustained slow-release formulation will have a lower

Table 1 **Lithium in mood disorders**

Bipolar disorder	
Acute mania	Lithium monotherapy is a first-line option Antimanic action can take 6–10 days In practice lithium is often used in combination with neuroleptics and/or benzodiazepines to achieve a more rapid effect
Acute depression	Lithium monotherapy is less effective in treating acute depression than it is in treating mania Effect of antidepressant action can take 6–8 weeks Often used to augment mood stabiliser or antidepressant therapy
Maintenance/prophylaxis	Lithium is superior to placebo and most anticonvulsants and neuroleptics used in the treatment of bipolar disorder Outcome is better if therapy is initiated early
Rapid cycling/mixed states	Lithium is shown to decrease symptom severity and reduce morbidity, but is less likely to achieve remission of symptoms and recovery
Major depression	
Acute	Lithium monotherapy is superior to placebo but it is rarely used, particularly in acute settings Greater efficacy for patients with a family history of bipolar disorder
Chronic	Often used as an augmentation strategy Effective in combination with all antidepressants and can be prescribed adjunctively with all treatment modalities

peak plasma concentration which may be better tolerated by some patients. After oral administration lithium is absorbed in the gut and excreted wholly via the kidneys. It has very few interactions relating to hepatic metabolism. Steady-state lithium concentrations can usually be achieved after 4–5 days of daily administration. Lithium has a relatively narrow therapeutic index so it is important to maintain lithium plasma concentrations within a specific range for each individual to achieve a balance between efficacy and adverse effects.

To minimise adverse effects when starting lithium de novo it should be administered in small divided doses then titrated gradually to achieve plasma concentrations of 0.6–0.8 mmol/L, while monitoring for these effects. Concentrations of up to 0.8–1.0 mmol/L may be needed for lithium-naïve patients and for treating acute recurrence of mania. Recent long-term studies suggest that even relatively low concentrations (0.6–0.8 mmol/L) confer reasonable prophylaxis, and are better tolerated.

Maintenance and prophylaxis therapy

The primary aim of prophylaxis is to prevent the recurrence of symptoms while minimising adverse effects and maintaining compliance. Lithium can be given as a once-daily dose for maintenance therapy. Most importantly, plasma lithium concentrations should be optimised to the symptom profile of the individual. Patients more prone to developing depressive episodes may benefit from concentrations of 0.4–0.8 mmol/L, whereas those more likely to become manic may require concentrations of 0.6–1.0 mmol/L long term.

Short-term adverse effects

Tremor, general fatigue, diarrhoea, thirst, polyuria, nausea, headache and vomiting are common initially, but are usually transient (1–2 days) and dose dependent. Most of these adverse effects are associated with rapid changes in plasma lithium concentrations and therefore should be anticipated whenever the dose of lithium is altered, and especially when it is increased.[8] If adverse effects persist for weeks or are particularly troublesome, lithium should be decreased or stopped. In practice this is rarely necessary and lithium can usually be reintroduced while titrating the dose carefully.

Long-term adverse effects

There are several adverse effects associated with long-term use of lithium and regular patient monitoring is required (Table 2).

Kidneys

Lithium affects the concentrating ability of the kidney, leading to polyuria and secondary thirst, but it is controversial whether lithium causes irreversible kidney damage. Approximately 10% of patients on lithium are prone to developing diabetes insipidus.[9] It is this renal insufficiency which is often thought to contribute to end-stage renal failure. Patients with renal impairment may remain on lithium treatments with appropriate dosage adjustments.

Thyroid

Lithium also affects thyroid function reducing the availability of thyroxine. The incidence of hypothyroidism is six-fold higher in patients on lithium as compared to the general population. Hypothyroidism in turn increases the likelihood of developing clinical depression.[8] Patients on lithium should therefore be routinely assessed for hypothyroidism and treated with thyroxine replacement if indicated.[8] It needs to be stressed however that hypothyroidism is not a contraindication for therapy.

Parathyroid

Parathyroid function can also be compromised by lithium. Patients on lithium are therefore prone to develop hypercalcaemia secondary to elevated parathyroid concentrations. Hyperparathyroidism that produces significant hypercalcaemia is a possible contraindication for continuing lithium so there is a need to monitor plasma calcium concentrations.[10]

Weight gain

Modest weight gain of 1–2 kg is common (5%) in patients on long-term lithium therapy. The trajectory of weight gain is steep at the beginning but soon plateaus. Diet, exercise and lifestyle advice are essential when patients start treatment.

Teratogenic effects

It appears that the risk of teratogenic effects from lithium has been exaggerated in the past.[10] However, there is a small risk and lithium is best avoided during pregnancy. Management during pregnancy should be collaborative and requires careful informed consideration of the risks.

Toxicity and its management

In acute lithium intoxication, the increase in plasma concentrations (>2 mmol/L) can be potentially lethal. Once renal excretion reaches its maximum, lithium accumulates rapidly and symptoms worsen. However, high plasma concentrations may cause relatively mild symptoms, and in these instances individuals often recover without permanent neurological damage. This occurs because lithium can take up to 24 hours to cross the blood–brain barrier, and brain concentrations usually peak eight hours after oral administration.

With lifelong treatment, lithium can gradually accumulate within the brain and lead to chronic neural toxicity because it has a longer half-life in the brain than in plasma. Symptoms such as lethargy, drowsiness, muscle weakness and hand tremor are indicative of neural toxicity and can manifest even at therapeutic concentrations of lithium. Toxicity from chronic lithium use is also subject to increases in dose and individual factors such as diminished renal function and ageing which may result in increased plasma concentrations.

It is therefore essential to monitor patients for symptoms of toxicity and assess plasma lithium concentrations every 3–6 months. If toxicity occurs, treatment should be stopped and prompt action taken to prevent serious damage.

Monitoring lithium

While it is generally recommended that plasma lithium concentrations may be monitored every 3–6 months,[11] current evidence suggests that unless otherwise indicated, annual monitoring may be sufficient (Table 2).

Table 2 **Recommendations for monitoring patients on lithium**

Parameter	Investigation	When to monitor
Lithium	Plasma lithium concentrations *	Monitor closely for first few days and aim to achieve concentrations within the therapeutic range Monitor every 3–6 months for long-term lithium use
Renal function	Urea and creatinine	Baseline then at 6 months
	Electrolytes	Baseline then annually
Thyroid function	Thyroid stimulating hormone concentrations	Baseline then at 6 months Annually for long-term lithium use
Parathyroid function	Calcium concentrations	Baseline then annually
Weight	Waist circumference, body mass index	Baseline then annually

Adapted from guidelines from the International Society for Bipolar Disorders.[11] More frequent investigation may be required if clinically indicated or a change in mood state is observed.

* In the event of acute toxicity (>2 mmol/L), lithium should be ceased immediately and haemodialysis can be used to reduce lithium in the blood

Adherence

Adverse effects are the most commonly cited reason for poor adherence. Of these, weight gain is the most distressing.[8] Not surprisingly, individuals who report multiple adverse effects are less likely to be adherent, and additional factors such as stigma and acceptance of the illness are important to bear in mind.[12]

The need to take medication when symptom-free is a key concern. This viewpoint often reflects a degree of denial by the patient because they are feeling better. This is more evident in younger individuals, those who have been recently diagnosed, and those taking lithium long-term. Patients who are not in a strong doctor–patient relationship and those who are less informed about the disorder and its treatment are generally less adherent.

Enhancing adherence requires a multifaceted approach involving education and monitoring of the patient. Close monitoring of patients improves adherence in two ways. First, it allows tailoring of the therapeutic dose to suit the individual, so that therapeutic benefit is optimised and the likelihood of adverse effects is minimised. Second, regular monitoring increases contact and therefore patients are likely to receive more frequent supervision and better education concerning their illness and its management.

Other strategies include educating family and friends to recognise the early signs of relapse and using a suitable means to manage stressors. Caregiver support increases adherence.[13] Encouraging patients to make a firm commitment to treatment before it starts, and coupling pharmacotherapy with psychotherapy, have also been shown to improve patient outcomes.[8]

Conclusion

Lithium can be used as monotherapy or in combination with other medications for the treatment of bipolar disorder. It is most efficacious in maintenance and prophylaxis and is widely used as a mood stabiliser, and has efficacy in both poles of the disorder. It is important to monitor both response and adverse effects and to regularly measure the plasma concentrations of lithium. This ensures adequacy of treatment and enhances compliance. If used wisely, lithium is relatively well tolerated and not complex to administer. It remains one of a handful of potentially life-changing treatments in psychiatry. ⋖

Lithium is relatively well tolerated and not complex to administer

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FURTHER READING

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