Lithium in mood disorders: increasing evidence base, declining use?

ALLAN H. YOUNG and JUDITH M. HAMMOND

Summary Use of lithium for the treatment of bipolar disorder may be declining even as knowledge of the efficacy and side-effects of lithium has increased. Recent meta-analyses confirm the benefits of maintenance lithium treatment and show that it reduces suicide and suicidality. Psychiatrists should continue to utilise this efficacious treatment for bipolar disorder.

Declaration of interest None.

The use of lithium appears to be in decline, possibly because of insufficient training of psychiatrists in the use of lithium therapy and the aggressive marketing of alternative medications that are patentable and therefore more profitable (Fieve, 1999; Jefferson, 2005). A decline in lithium use has been demonstrated by empirical studies in the USA (Fenn *et al*, 1996; Blanco *et al*, 2002), Canada (Shulman *et al*, 2003), and Germany, Switzerland and Austria (Wolfsperger *et al*, 2007). In a study of prescription patterns for Americans with bipolar disorder in 2002–3, Baldessarini *et al* (2007) found that lithium was prescribed for only 7.5% of patients initially but was retained in monotherapy for much longer than other treatments, which were augmented or discontinued. The decline in lithium use is not universal; lithium use has increased in Spain (Castells *et al*, 2006) and remains high in England, where a recent study found that approximately half of patients with bipolar disorder are prescribed lithium (Anderson *et al*, 2004).

PROPHYLAXIS

The decline in lithium use has occurred as the evidence base supporting its use has strengthened. Although the efficacy of lithium in treating acute mania is long-established, doubts remained about its prophylactic efficacy until recently. Recent regulatory clinical trials of new medications for bipolar disorder have included lithium as a gold-standard comparator and Smith *et al* (2007) used these studies in a meta-analysis evaluating the effectiveness of lithium as a maintenance treatment in this disorder.

This meta-analysis of 14 randomised controlled trials, of which 8 included placebo arms, provides strong evidence for the prophylactic efficacy of lithium, which prevented relapse to any mood episode with a hazard ratio of 0.68 (95% CI 0.53–0.86; Smith *et al*, 2007). The overall prophylactic efficacy of lithium was largely explained by the reduction in manic relapses (hazard ratio 0.53, 95% CI 0.35–0.79). Lithium-treated patients also had fewer depressive relapses, but this effect was smaller and not statistically significant.

The efficacy of lithium in bipolar disorder is recognised by the most recent evidence-based clinical guidelines for bipolar disorder, which recommend it as a first-line treatment (Canadian Network for Mood and Anxiety Treatments, 2006; National Institute for Health and Clinical Excellence, 2006).

SUICIDAL BEHAVIOUR

In two recent meta-analyses lithium has also been shown to reduce the incidence of suicide and suicidality in people with mood disorders (Cipriani *et al*, 2005; Baldessarini *et al*, 2006). In their meta-analysis of randomised controlled trials Cipriani *et al* (2005) found that lithium reduces the risk of suicide (odds ratio 0.26, 95% CI 0.09–0.77, P=0.01) and self-harm (assessed with suicide in composite outcome, odds ratio 0.21, 95% CI 0.08–0.50, P=0.0005) among patients with mood disorders. Baldessarini *et al* (2006) included open-label studies as well as randomised controlled trials in their meta-analysis. Overall, long-term lithium treatment resulted in a 4.91-fold (95% CI 3.82–6.31, $P<0.0001$) lower risk of suicidal acts or an 80% sparing of risk. A subgroup analysis showed that the reduction in suicidal acts occurred in studies that included only patients with bipolar disorder as well as studies including a mix of patients with major affective or schizoaffective disorders. In addition to decreasing the rate of suicidal acts, lithium appears to reduce the 'lethality of suicide', as indicated by the ratio of attempted to completed suicide. This ratio is usually much lower for people with bipolar disorder (5:1) than the general population (20–30:1), and lithium treatment increases it by about 2.9 times. The efficacy of lithium in reducing suicidal behaviour in spite of its limited prophylactic effect for bipolar depression suggests that its anti-suicidal action might operate via domains other than depressed mood, possibly by an effect on impulsivity and aggression (inward or outward), both common in bipolar disorder and both potential influences of suicidal behaviour (Baldessarini *et al*, 2006).

TREATMENT ADHERENCE

Patients' adherence to lithium treatment is of utmost importance because discontinuation increases the risk of manic relapse (Goodwin, 1994). Although lithium reduces the risk of suicide in bipolar disorder, suicide rates remain elevated. Gonzalez-Pinto *et al* (2006) recently demonstrated that adherence to lithium prophylactic treatment may be correlated with suicide risk. Suicidal acts (including attempts and completed suicides) occurred in 12.5% of patients adhering to lithium treatment and 43.8% of those not adhering (χ^2=7.76, P=0.005). Treatment adherence was a strong predictor of suicidal behaviour, even after controlling for effects of other risk factors, such as age, previous episodes and number of depressive episodes (Gonzalez-Pinto *et al*, 2006). Adherence is potentially modifiable: thus suicidal behaviour may be further reduced. Colom *et al* (2003, 2005) evaluated the effect of a 21-session structured group psychoeducation programme on patient outcome and serum lithium levels in euthymic patients with bipolar disorder over a 2-year period. Serum lithium levels in the 49 patients who received psychoeducation were significantly higher and more stable than in the 44 patients assigned to the control group (Colom *et*

al, 2005). Moreover, patients receiving psychoeducation experienced significantly fewer manic and depressive relapses (Colom *et al*, 2003).

IS LITHIUM TOO TOXIC?

One reason for the decline in lithium use might be that it has a reputation among psychiatrists as a toxic drug that is difficult to use. Indeed, monitoring serum lithium levels is necessary in order to optimise treatment efficacy as well as prevent lithium toxicity. Patients prescribed lithium for the first time should have serum lithium levels measured once a week until levels have stabilised between 0.6 and 0.8 mmol/l. For patients who still have sub-threshold symptoms with functional impairment after 6 months with these lithium levels, and for those who have previously relapsed while on lithium treatment, a 6-month trial of higher doses resulting in stable serum lithium levels of 0.8 to 1.0 mmol/l should be considered (National Institute for Health and Clinical Excellence, 2006). Uncertainty remains about what is the ideal therapeutic level of lithium and there is surprisingly little published evidence on this topic; further research is required in this area.

However, this is not a reason to neglect lithium: assessing serum levels of lithium is fast, simple, accurate and inexpensive. Furthermore, because the side-effects of lithium have been studied for decades, there are comprehensive guidelines for the prevention, monitoring and treatment of adverse effects (Canadian Network for Mood and Anxiety Treatments, 2006; National Institute for Health and Clinical Excellence, 2006). Of particular concern is lithium's potential for nephrotoxicity. The risk of adverse renal effects can be ameliorated with preventive measures, vigilance and appropriate treatment and should not contraindicate lithium treatment. Lithium can affect either tubular or glomerular kidney function (Young & Macritchie, 2004). In tubular dysfunction, which is more common, the kidney's ability to concentrate urine is reduced (Young & Macritchie, 2004). Diabetes insipidus is marked by polyuria and polydypsia, and can progress to severe dehydration; furthermore, the intraluminal lithium concentration can increase to toxic levels. Monitoring for diabetes insipidus, the most common renal complication of lithium therapy, is vital because it is initially reversible on lithium withdrawal but may become irreversible as a result of structural damage. Annual assessment of urine production, which should not exceed 41 in 24 h, is mandatory. In addition, patients should be advised to see their doctor if they find they become excessively thirsty. Although it is not possible to guarantee prevention of lithium-induced diabetes insipidus, the risk is reduced by employing the lowest therapeutic dose of lithium. In some instances, lithium-induced diabetes insipidus can be managed entirely by dose reduction, although combination therapy or lithium substitution is necessary in others. Severe acute diabetes insipidus must be treated by a renal specialist because restoration of water and electrolyte levels is urgent in order to prevent lithium toxicity, neurological impairment and encephalopathy.

More rarely, lithium affects glomerular function, causing the glomerular filtration rate to decline, which can compromise waste elimination and fluid–electrolyte homoeostasis. Although glomerular dysfunction appears to be uncommon, it is advisable to conduct a baseline assessment of renal function before initiating lithium treatment, including measurement of serum electrolytes and creatinine, urinanalysis and blood urea nitrogen. Chronic renal failure may be asymptomatic in the early stages, so it is vital to monitor serum creatinine at least every 6 months. Serum creatinine is a crude measure of glomerular filtration rate and increasing creatinine levels and/or levels greater than 140 μmol/l signal a need for further assessment.

IS LITHIUM NEUROPROTECTIVE OR NEUROTOXIC?

There has been some debate as to whether long-term lithium therapy is neuroprotective or neurotoxic. Putative neuroprotective effects include blocking accumulation of the amyloid-beta peptides that overproduce amyloid precursor protein in the brains of people with Alzheimer's disease, inhibiting hyperphosphorylation of tau (the main component of neurofibrillary tangles; Terao *et al*, 2006), antagonising vinca alkaloid neurotoxicity (which induces peripheral neuropathy and muscle damage; Petrini *et al*, 1999), increasing levels of *N*-acetyl-aspartate in all brain regions (a potential marker of neuronal viability and function; Moore *et al*, 2000*a*) and increasing grey-matter volume (Moore *et al*, 2000*b*; Beyer *et al*, 2004). Reported neurotoxic effects include reversible changes in the clinical electroencephalogram (Struve, 1987), slowing of motor and sensory nerve conduction (Chang *et al*, 1990) and impairment of cerebellar control of fast single-joint movement (Setta *et al*, 1998). There is contradictory evidence as to whether lithium therapy increases (Dunn *et al*, 2005) or decreases (Terao *et al*, 2006) the risk of dementia. A beneficial effect of lithium on dementia risk is suggested by the report that elderly patients with bipolar disorder (who usually have an increased risk of Alzheimer's disease) had the same prevalence of Alzheimer's disease as the general elderly population when treated with lithium (Nunes *et al*, 2007).

Fountoulakis *et al* (2007) conducted a literature review and concluded that the data concerning the neuroprotective/neurotoxic effect of lithium therapy is 'unclear or conflicting', since there is conflicting evidence from uncontrolled non-randomised studies and from animal and basic scientific studies. They therefore recommend maintaining the clinical guidance to use lithium at the lowest therapeutic levels.

CONCLUSIONS

In recent years the number of pharmacological agents available for treating patients with bipolar disorder has increased significantly and some patients may be best treated by agents other than lithium. However, lithium continues to be the most effective and best-tolerated treatment option for many patients. Psychiatrists should continue to include this efficacious treatment in their arsenal for bipolar disorder.

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ALLAN H. YOUNG, MB, ChB, MPhil, PhD, FRCPsych, FRCPC, Institute of Mental Health, JUDITH M HAMMOND, BA, MSc, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence: Professor Allan H. Young, Institute of Mental Health, University of British Columbia, University Boulevard, Vancouver, British Columbia, Canada V6T 1Z3. Email: allan.young@ubc.ca

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