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Old drug, new data

Revisiting... Lithium therapy

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Abstract New data have emerged over the past 10 years regarding the efficacy and mechanisms of action of lithium. This article briefly summarises the evidence for the use of lithium to treat affective disorders and psychosis, reviews its putative anti-suicidal effect, highlights new research on its mechanism of action and provides an update on some important side-effects and consequences of its use.

The authors revisit a topic considered in the first volume of APT (Ferrier et al, 1995). That 1995 article is available on our website (http://apt.rcpsych.org) as a data supplement to the online version of the present submission.

Lithium remains a mainstay in the acute and prophylactic treatment of bipolar affective disorder. It is used in the augmentation of antidepressant treatment and, less frequently, in the augmentation of antipsychotic treatment of schizophrenia. It is reported to have specific anti-suicidal effects. Systematic reviews by the Cochrane Collaboration and others have examined the evidence base for its use in these contexts. A brief summary of their findings is given here.

Evidence of efficacy

Maintenance treatment

In a systematic review Burgess *et al* (2001) investigated the efficacy of lithium in preventing recurrence of mood disorders. They included nine randomised placebo-controlled studies of lithium involving a total of 825 participants. About half of the trials had recruited people with bipolar disorder, and the remainder studied people with unipolar disorder or mixed groups with either unipolar or bipolar disorder. Participants received treatment for at least 3 months and blood serum lithium concentrations ranged from 0.5 to 1.4 mmol/l. Lithium had greater efficacy than placebo in relapse prevention for mood disorders in general, but the effect size was modest. The most consistent effect was found in bipolar disorder. In unipolar disorder, the trend favoured lithium, but its effect was not statistically significant.

Treatment and prevention of mania

In the treatment of mania, one randomised controlled trial (Bowden *et al*, 1994) found that a greater proportion of patients responded to lithium than to placebo. Geddes (2004) summarised the data from systematic reviews and from randomised controlled trials using lithium in comparison with other active agents. Lithium was superior to chlorpromazine but less effective than risperidone in reducing manic symptoms. The data did not demonstrate a significant difference in antimanic efficacy between lithium and haloperidol, carbamazepine or valproate.

Two agents, lamotrigine and olanzapine, merit more detailed discussion, as new evidence has emerged. Three randomised controlled trials have examined lamotrigine's efficacy in mania. Although Ichim *et al* (2000) found no difference in antimanic effect between lithium and lamotrigine, two unpublished studies in mania found no significant difference between lamotrigine and placebo (GlaxoSmithKline Clinical Trial Register: http://ctr.gsk.co.uk/Summary/lamotrigine/studylist.asp). Goodwin *et al* (2004)

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found that lithium had prophylactic efficacy against mania, prolonging the time to intervention in a pooled analysis of two placebo-controlled 18-month trials of lamotrigine and lithium in bipolar I disorder. Although both lithium and lamotrigine delayed the time to treatment for any mood episode, lamotrigine showed a more robust effect in preventing depression than mania.

In studies comparing lithium and olanzapine, one 4-week randomised controlled trial found no significant difference in their effects in the treatment of mania (Berk *et al*, 1999). A 12-month study comparing these agents in maintenance treatment of people recently recovered from mania revealed some benefit for olanzapine (Tohen *et al*, 2005): it was significantly more effective in preventing mania and mixed episode recurrence, but not in preventing depression. It was also associated with significantly more weight gain.

Treatment of bipolar depression

Although several expert guidelines recommend lithium for the treatment and prevention of depression in bipolar disorder, the evidence from randomised controlled trials for its use in acute bipolar depression is surprisingly limited. It is based on a small number of early placebo-controlled trials, none of which is of parallel-group design. A relatively recent systematic review on bipolar depression found no randomised controlled trials to be of methodological quality sufficient to provide reliable evidence of its efficacy (Nolen & Bloemkolk, 2000). However, lack of evidence does not in itself establish lack of effectiveness and there is indirect evidence of lithium's efficacy in this context. For instance, in one study, people in the depressed phase of bipolar disorder with high serum lithium levels showed no significant difference in response rates from those treated with antidepressants (Nemeroff *et al*, 2001). Its prophylactic efficacy against depressive recurrence also suggests antidepressant activity (Burgess *et al*, 2001).

Augmentation in treatment-resistant depression

Bauer & Döpfmer (1999) found evidence in support of lithium augmentation in the treatment of refractory depression. Their systematic review included nine randomised placebo-controlled trials, with a total of 234 patients. The duration of treatment ranged from 2 to 42 days. In three trials, a minimum daily dose of 800 mg was used or a target serum lithium concentration of greater than 0.5 mEq/l was achieved for 2 weeks: lithium augmentation led to a significantly higher response rate than placebo. When all nine studies were entered into a cumulative meta-analysis in order of increasing dose, the effect of lithium treatment was statistically significant at a daily dose of 600–800 mg. Bauer & Döpfmer concluded that lithium augmentation increased treatment response in people with refractory depression.

Schizophrenia

The efficacy of lithium in schizophrenia was analysed by Leucht *et al* (2004). They identified 20 randomised controlled trials, involving 611 participants, comparing lithium with antipsychotics or placebo. They found no evidence that lithium monotherapy is an effective treatment for schizophrenia. The evidence available on augmentation of antipsychotics with lithium was inconclusive.

Anti-suicidal effects

The anti-suicidal effects of lithium have been debated over the past 30 years. Tondo *et al* (2001) sought studies on lithium treatment in people with bipolar disorder, major affective disorder and schizoaffective disorder which reported data on suicide rates. They identified 22 studies, involving a total of 5647 participants with 33 473 patient years. Only three of the studies were randomised. For comparison, they used data from 13 studies reporting suicide rates for patients who were not receiving lithium treatment over a mean period of 5 years. The suicide rate in the groups receiving lithium treatment was significantly lower than that in groups without lithium. Results consistent with a protective effect against suicide were also found when the analysis was restricted to the three randomised trials. A recent meta-analysis of 12 randomised studies reporting suicide rates in people with mood disorders provides new support for the protective effect of lithium in this context (Cipriani *et al*, 2005).

In a narrative review Muller-Oerlinghausen *et al* (2005) summarised the evidence for lithium's effects against suicide and suicidal behaviour in affective disorders, concentrating on bipolar disorder. The following interesting questions were raised: is the putative anti-suicidal effect of lithium specific to lithium and does it occur outwith improvements in affective symptoms?

In discussing whether the anti-suicidal effect of lithium is shared by other psychotropic agents, the authors cited two randomised controlled trials. First, a randomised prospective study compared lithium with carbamazepine in the treatment of bipolar and schizoaffective disorders over 2½ years (Multicenter Study of Long-term Treatment of Affective and

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Schizoaffective Psychoses (MAP); Thies-Flechtner *et al*, 1996). There were significantly more suicides and suicide attempts in the carbamazepine group. Second, Goodwin *et al* (2003) conducted a retrospective review of suicide risk in patients on lithium compared with those on valproate and those on carbamazepine. The adjusted suicide risk for the valproate group was 2.7 times higher than that for the lithium group. The study was insufficiently powered to allow similar comparisons for carbamazepine.

Does lithium have an anti-suicidal effect independent of its effects in episode treatment and prevention? Ahrens & Muller-Oerlinghausen (2001) conducted a sub-analysis of data from the International Group for the Study of Lithium-treated Patients. They selected individuals with recurrent affective disorders and at least one suicide attempt before the onset of lithium treatment (a total of 176) and divided them into three groups on the basis of their response to lithium (excellent, moderate or poor). A statistically significant reduction in suicide attempts was found in all three groups, even those who were considered to have responded poorly to treatment. Although clearly not conclusive, these data support an independent suicidal effect for lithium.

Summary of the evidence

Box 1 summarises the evidence base from systematic reviews of lithium in affective disorders, psychosis and against suicide.

Box 1 Summary of the evidence

Current systematic reviews of lithium studies suggest the following:

Affective disorders

- Lithium is an efficacious maintenance treatment for bipolar disorder, but the evidence for its prophylactic efficacy in unipolar disorder is less strong
- It is efficacious in the treatment of mania
- Its use in bipolar depression requires more methodologically rigorous examination
- Lithium augmentation increases treatment response in refractory depression

Psychoses

- Lithium monotherapy is not an effective treatment for schizophrenia
- The evidence on its use in the augmentation of antipsychotics is inconclusive

Anti-suicide effect

- Lithium has a protective effect against suicide and suicidality that may be directly pharmacological, rather than the consequence of symptom improvement or dependent on prolonged use in treatment-adherent patients

Mechanism of action: progress on understanding

Despite lithium's established therapeutic efficacy, details of its therapeutic mechanism of action are yet to be determined. Lithium has been shown to produce a number of biochemical effects, including effects on monoamines, other neurotransmitters, second messengers and regulators of intracellular signalling (Table 1). However, which, or which combinations of, effects contribute to its therapeutic response(s) remains unclear.

Monoamine neurotransmitter systems

Because of the implication of monoamine neurotransmitter systems in the aetiology of the major psychiatric disorders, the interaction between lithium and monoamine neurotransmission has been the focus of much attention. Studies have revealed that lithium has the ability to modulate a number of components of central monoamine neurotransmission. However, much of this work is old and has inconsistencies, with different studies producing contradictory results, suggesting a need for more work to be carried out.

Preclinical and clinical studies suggest that, in the short term, lithium can increase serotonergic neurotransmission (Price *et al*, 1990; Shiah & Yatham, 2000). However, this effect is not always evident after long-term treatment and therefore the implications of this in the mechanism of action of lithium in long-term treatment and in its anti-suicide effect are unclear (Lenox & Manji, 1995). Furthermore, some studies have indicated a decrease in serotonergic neurotransmission after lithium treatment. These conflicting results are probably due to major differences in methodologies (administration, brain region, dose regimens, etc.).

Lithium can also affect the dopaminergic system. Acute administration of lithium has been shown to produce a decrease in dopamine neurotransmission that may link to its antimanic effect (Berggren, 1985). However, chronic administration of lithium has little consistent effect on dopamine turnover (Ferrie *et al*, 2005). Chronic lithium treatment does prevent behavioural and biochemical manifestations of haloperidol-induced dopamine receptor supersensitivity (Lenox & Ha hn, 2000). It appears that

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Table 1 Summary of the main neurobiological effects of lithium

System	*Effect of lithium*	*Reference*
5-HT (serotonin) function	Greatly increased	Price *et al*, 1990; Shiah & Yatham, 2000
Acetylcholinesterase function	Greatly increased	Dziedzicka-Wasylewska *et al*, 1996; Kameda *et al*, 2001
Sodium function	Increased	Wood & Goodwin, 1987
Dopamine function	Reduced	Dziedzicka-Wasylewska *et al*, 1996; Kameda *et al*, 2001
GABA function	Increased	Motohashi, 1992; Antonelli *et al*, 2000
Inositol	Reduced	Hallcher & Sherman, 1980
cAMP	Reduced	Goldberg *et al*, 1988; Chen *et al*, 2000
Protein kinase C	Reduced	Manji & Lenox, 1999; Wang *et al*, 2001
Glycogen synthase kinase	Greatly reduced	Ryves & Harwood, 2001
Brain-derived neurotrophic factor	Increased	Mai *et al*, 2002; Chuang, 2004
Bcl-2	Increased	Manji & Chen, 2002
Pro-aptotic proteins (p53, BAX)	Reduced	Chuang *et al*, 2002

this effect is mediated presynaptically, since lithium treatment has not been shown to result in any consistent change in D_1 or D_2 receptor regulation, which would have suggested a postreceptor site of lithium action (Dziedzicka-Wasylewska *et al*, 1996).

Clinical evidence suggests that the neurotransmission imbalance implicated in affective illness is related to excessive dopaminergic activity but also to a reduced cholinergic activity (Bymaster & Felder, 2002). Chronic lithium administration produces an upregulation of muscarinic receptors in the rat brain (De Bruin *et al*, 2000). Studies have also shown that lithium treatment enhances various behavioural responses that are cholinergically mediated. Thus, lithium reduces the convulsant threshold to the non-specific cholinergic muscarinic agonist arecoline and to anticholinesterases (Jope, 1993). There are also reports (Wang *et al*, 1997) that show that the sensitivity of central nicotinic receptors is decreased following lithium administration.

Although relatively less attention has been paid to the effects of lithium on amino acid and neuropeptide regulation in the brain, investigators have reported that lithium produces elevations in γ-aminobutyric acid (GABA) in the striatum and midbrain (Ahluwalia & Singhal, 1981). An increase in GABA turnover in the hippocampus and striatum following lithium treatment has also been reported (Motohashi, 1992). This may be clinically important in bipolar disorder, given GABA's inhibitory actions.

Effect on second messengers/intracellular signalling

In recent years, it has become increasingly appreciated that modulation of neurotransmitter function and neuronal activity by intracellular signalling systems is a possible therapeutic action of lithium. It has long been established that lithium inhibits the intracellular enzymes inositol monophosphatase, cyclic adenosine monophosphate (cAMP) and protein kinase C, and consequently has numerous effects on neuronal activity that may link to its unique clinical profile (Gurvich & Klein, 2002).

More recently, lithium has been shown to be an inhibitor of glycogen synthase kinase-3β (GSK-3β). This enzyme is an important mediator of a number of cellular processes, including regulation of transcription factors associated with apoptosis and neuronal plasticity. This may be the mechanism whereby lithium protects rat brain neurons in culture from glutamate-induced *N*-methyl-D-aspartate (NMDA) receptor-mediated excitotoxicity. This neuroprotection is accompanied by upregulation of the anti-apoptopic factor Bcl-2 and activation of other cell survival factors. Lithium also induces the expression of brain-derived neurotrophic factor (BDNF) and subsequent activation of Trk-B, the BDNF receptor. The activation of BDNF/Trk-B signalling is likely to be the mechanism of the neuroprotective effects of lithium that have been shown in rodent models of disease such as the rat model of stroke (Chuang, 2004). Whether these effects are seen in patients on lithium is not yet clear and the clinical significance of changes in cell signalling remains to be determined. However, there is preliminary evidence that lithium induces increases in grey-matter volume after 4 weeks in people with bipolar disorder (Moore *et al*, 2000). These changes may be particularly significant given the increasing evidence of structural changes in the brain and associated neuropsychological deficits even in euthymic bipolar disorder (Thompson *et al*, 2005).

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It is now accepted that lithium can regulate multiple targets. Some of these have been described above, but we are still some away from delineating just how the different actions of lithium combine to achieve its mood-stabilising effects.

Adverse effects

Lithium has a narrow therapeutic index and a number of adverse effects that often result in poor adherence to treatment (McCreadie *et al*, 1985). Table 2 outlines the more common or important non-toxic adverse effects, with their usual time of onset and relationship to serum levels. In the initial phase of treatment, thirst, abdominal discomfort, nausea, diarrhoea, gustatory disturbance, muscle weakness and fatigue may be troublesome. These symptoms occur more frequently at higher serum lithium levels. They tend to be transitory and are to be distinguished from symptoms of toxicity and from problematic longer-term effects such as tremor, diabetes insipidus, renal impairment and hypothyroidism.

Since the publication of our original review (Ferrier *et al*, 1995) new information on adverse effects has become available. We give below a brief review of our current knowledge and discuss new findings on lithium toxicity and renal impairment. We also review the clinical implications of the lithium 'rebound' phenomenon, an important adverse effect.

Lithium toxicity

Lithium toxicity (lithium intoxication) varies in presentation. Acute toxicity can occur in lithium-naïve individuals or after a long, uneventful course of treatment. It can occur at therapeutic serum levels, and it can arise following a change in dose or the introduction of new medication. Chronic toxicity can be insidious but its effects are potentially serious.

Mild toxicity is characterised by nausea, diarrhoea, blurred vision, polyuria, dizziness, a fine resting tremor, muscle weakness or drowsiness. Cerebellar signs are a core feature of lithium neurotoxicity. With increasing severity, parkinsonism and chorea may occur, indicating basal ganglia involvement. Confusion, blackouts, fasciculation, hyper- reflexia, incontinence and hypernatraemia may develop. In severe cases, acute renal failure, hypotension or hypertension occur. Electrocardiogram changes include sinus and junctional bradycardia and heart block. Impaired consciousness, seizures and coma may progress to death. Neurotoxic effects may be insidious in onset. A persistent cerebellar ataxia has been reported in the absence of overt toxicity (Lang & Davis, 2002).

Risk factors

Risk factors for lithium toxicity include factors that in themselves lead to increments in lithium serum levels and those that predispose to lithium toxicity at a given level. Nephrogenic diabetes insipidus and impaired creatinine clearance may result in increased lithium levels at a given dose. Similarly, drug interactions predisposing to toxicity include medications that cause hyponatraemia and reduced lithium clearance, for example frusemide, thiazide diuretics and some antidepressants. Angiotensin-converting enzyme (ACE) inhibitors reduce glomerular perfusion pressure and may enhance the tubular reabsorption of lithium. An

Table 2 Early-, medium-term and late-onset side-effects of lithium, not associated with toxicity

Early (1–14 days)	*Medium term (14–365 days)*	*Late (>365 days)*
Related to high lithium level (≥0.8 mmol/l)		
Gastrointestinal: anorexia; bad taste in mouth; diarrhoea	Gastointestinal: vomiting; dry mouth	Cognitive: slow reaction times; impaired memory
	Renal: polyuria; nephrogenic diabetes insipidus	Renal: impairment
	Neurological: tremor	Neurological: myopathy; ataxia
	Cardiac: T-wave inversion; dysrhythmia	
	Dermatological: worsening of skin diseases, e.g. psoriasis	
Not related to high lithium level		
Thyroid: reduced T_4 (transient)	Thyroid: non-toxic goitre; hypothyroidism; hyperthyroidism (rare)	Metabolic: weight increase
	Gastrointestinal: persistent mild diarrhoea	
	Haematological: leucocytosis	
	Neurological: weakness	

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important, potentially toxic, interaction is between lithium and non-steroidal anti-inflammatory drugs. Factors predisposing to lithium toxicity at a given dose include pre-existing brain injury and physical illnesses such as hypertension, diabetes and congestive cardiac failure.

Diagnosis, treatment and sequelae

Patients with suspected lithium toxicity should be observed for at least 24 h. Lithium should be stopped, or the dose reduced. Lithium levels should be monitored immediately and then every 6–12 h, depending on the presentation. The diagnosis of lithium toxicity is made on clinical grounds. A therapeutic level does not exclude toxicity. Serum lithium levels should not be used as the only guide to the severity of poisoning, as lithium absorption from the gastrointestinal tract and release from intracellular stores may be prolonged. Lithium excretion is greatly diminished in cases of toxicity, further compounding the problem.

In mild cases, attention to hydration, electrolyte balance and electrocardiogram (ECG) monitoring is necessary. In more severe cases, haemodialysis should be considered: it should be instituted when serum lithium levels are greater than 3 mmol/l, in cases of coma or shock, or when conservative measures have failed. It is essential to observe symptom progression over time. Clinical improvement may take up to 3 weeks. Neurological symptoms occasionally persist, usually in the form of cerebellar symptoms, with the possibility of improvement over the following year. Persistence of neurological symptoms is more likely in more severe and prolonged cases of acute toxicity. The most commonly reported irreversible sequel of lithium neurotoxicity is persistent cerebellar dysfunction (Adityanjee *et al*, 2005).

Renal impairment

Lithium therapy may result in renal impairment through its effects on tubular or glomerular function. These will be considered in turn.

Tubular dysfunction

Diabetes insipidus is characterised by polyuria and polydipsia. It results from renal tubular dysfunction or from inadequate pituitary production of antidiuretic hormone. Lithium-induced diabetes insipidus is predominantly nephrogenic in origin (Bendz & Aurell 1999), although case reports of the neurogenic form exist (Posner & Mokrzycki, 1996). The kidney loses its ability to concentrate urine. Risk factors include a long duration of treatment and polypharmacy. It may occur less frequently with once-daily dosing (Bowen *et al*, 1991). Diagnosis is confirmed through the water deprivation test and the desmopressin (DDAVP) test.

In mild, reversible cases, simple lithium dose reduction or once-daily dosing may be adequate. Alternative strategies include combination psychotropic treatment or lithium substitution. In severe cases of acute diabetes insipidus, marked dehydration may occur (Bendz & Aurell, 1999), necessitating referral to a renal physician. The priority is the restoration of water and electrolyte balance. In severe cases, the potential for lithium toxicity (exacerbated by dehydration), neurological impairment and encephalopathy should be recognised. Thiazide diuretics, although effective, should be avoided if possible, because an associated increased sodium and lithium reabsorption may lead to lithium toxicity.

Patients on long-term treatment may suffer a progressive urinary-concentrating impairment which is not fully reversible on stopping treatment. This impairment is thought to be due to irreversible underlying renal damage, and not to nephrogenic diabetes insipidus. There are reports of a correlation between impaired concentrating ability and the duration of lithium treatment (Hestbech *et al*, 1977). Hansen *et al* (1979) suggested an association between this functional impairment and chronic interstitial nephropathy.

Chronic interstitial nephropathy is frequently reported in lithium-associated renal disease. Its histopathological features include tubular atrophy and interstitial fibrosis. Although these features have been found in psychiatric patients who have never received lithium, distal tubular dilatation and microcyst formation appear to differentiate the lithium-treated group. Markowitz *et al* (2000) demonstrated that lithium-associated chronic tubulo-interstitial nephropathy may lead to renal insufficiency and renal failure, despite the discontinuation of treatment.

Glomerular dysfunction

The incidence of lithium-induced glomerular impairment is unclear owing to methodological inconsistencies between studies. The literature on lithium-induced glomerulosclerosis has been largely confined to case reports (Santella *et al*, 1988). However, a newer study on 24 patients with lithium nephrotoxicity found focal segmental glomerulosclerosis correlating with proteinuria (of >1 g/dl) in half of the sample (Markowitz *et al*, 2000). These people had been treated with lithium for a mean of 13.6 years (range 2–25 years). They all presented with renal insufficiency. Only two were known to have had previous episodes of acute lithium intoxication. These findings require confirmation in other studies, but it is possible that the incidence of lithium-induced glomerular toxicity has been underestimated.

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Clinical implications

Clinicians should remain alert to the possibility of renal failure in patients on lithium treatment. Acute renal failure associated with lithium toxicity may present with acute oliguria, fluid retention, uraemia and associated nausea and vomiting. Chronic renal failure may be asymptomatic in the early phases, with insidious onset of hypertension, thirst, polyuria and proteinuria. Risk factors for renal impairment include long duration of therapy, concomitant use of other medications, episodes of lithium toxicity and other coexisting medical conditions.

In patients with evidence of renal impairment, lithium levels should be monitored regularly (at least every 2 months) and kept at the lower end of the therapeutic range. Once-daily dosing is recommended. Measurement of 24 h urinary volume and creatinine clearance should be considered annually. In acute renal failure, an urgent nephrology opinion is indicated. Lithium should be stopped and an alternative treatment instituted, with appropriate dose adjustment for the degree of renal failure. Close collaboration with renal physicians may be required in the case of those in whom the benefits of treatment must be weighed against compromised renal function.

'Rebound' affective episodes on lithium discontinuation

Abrupt discontinuation of lithium prophylaxis may precipitate early recurrence of mania and depressive episodes (Mander & Loudon, 1988; Suppes *et al*, 1991). This occurrence, called the rebound phenomenon, presents a significant clinical problem. Goodwin (1994) argued that it may negate the benefits of lithium treatment altogether in bipolar disorder. Using data from Mander & Loudon (1988) he calculated that, given the risk of precipitating early recurrence on its withdrawal compared with the risk of recurrence in the untreated group, lithium prophylaxis must be maintained for at least 24 months before an overall advantage is conferred. It appears that there is an earlier and greater risk of mania than of depression on lithium withdrawal (Mander & Loudon, 1988; Suppes *et al*, 1991). Discontinuation of lithium may result in resistance to subsequent treatment with the drug, although this possibility is disputed (Coryell *et al*, 1998). There is also evidence that abrupt reduction of the dose of lithium should be avoided, as the relapse rate increases under this circumstance (Perlis *et al*, 2002).

Patients should be advised that abrupt discontinuation of lithium carries a high risk of manic recurrence. Gradual discontinuation over 4 weeks may lead to a lower recurrence rate (Faedda *et al*, 1993).

Conclusions

Lithium remains one of the most important weapons in our psychopharmacological armamentarium. Recent research has confirmed its efficacy in mania and in prophylaxis in bipolar disorder, and its useful role in treatment-resistant depression. There are also new insights into potential clinical benefits as a neuroprotective agent and as a way of reducing suicidal behaviour and suicide itself.

However, there is also an increasing understanding of the real and potential hazards of lithium therapy, including insidious and irreversible neuro- and nephrotoxicity. It is difficult for many patients to take the drug and, unfortunately, stopping it is not a neutral act – there are potential consequences so that the patient can be worse off than if they had never received lithium in the first place. Perhaps the way out of this dilemma – an effective evidence-based treatment but with significant negative consequences – lies in preclinical research, some of which is reviewed here. This work holds out the prospect of understanding lithium's mechanism(s) of action with the hope of thereby boosting its positive effects and diminishing the negative aspects, and/or the development of new, more effective but less toxic drugs.

Declaration of interest

None.

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MCQs

1 The evidence base provides clear evidence that lithium is an efficacious treatment in the following situations:
a prophylactic treatment of bipolar disorder
b prophylactic treatment of unipolar disorder
c treatment of mania
d treatment of bipolar depression
e in monotherapy for schizophrenia.

2 The following are associated with severe lithium toxicity:
a cerebellar signs
b sinus and junctional bradycardia
c hypotension
d fine resting tremor
e acute renal failure.

3 Regarding the management of lithium toxicity:
a patients with suspected lithium toxicity should be observed for at least 24 h
b a therapeutic level excludes toxicity
c serum lithium levels provide the only necessary guide to the severity of poisoning
d lithium excretion may be diminished in toxicity
e cerebellar symptoms may persist for months.

4 Regarding diabetes insipidus:
a it is characterised by polyuria and polydipsia
b it always results from renal tubular dysfunction
c it is usually neurogenic in origin when induced by lithium
d it may be diagnosed through the water deprivation test and the desmopressin (DDAVP) test
e polypharmacy including lithium is not a risk factor.

5 Regarding the lithium rebound phenomenon:
a abrupt discontinuation of lithium prophylaxis may precipitate early depressive recurrence in bipolar disorder
b the risk of depression is earlier and greater than the risk of mania
c Goodwin calculated that lithium prophylaxis for bipolar disorder must be maintained for at least 6 months before an overall advantage over no treatment is conferred
d the development of resistance to lithium treatment following discontinuation is an established clinical phenomenon
e gradual discontinuation of lithium has been demonstrated to lead to a higher rate of episode recurrence than abrupt withdrawal.

MCQ answers

1	2	3	4	5
a T	a T	a T	a T	a T
b F	b T	b F	b F	b F
c T	c T	c F	c F	c F
d F	d F	d T	d T	d F
e F	e T	e T	e F	e F

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