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Editorial

More good news about the magic ion: lithium may prevent dementia†

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Summary
Lithium is an established treatment for affective disorders with good evidence of antisuicidal properties. Alzheimer's disease rates are relatively reduced in patients with bipolar disorder on lithium and a recent trial of lithium in amnestic minimal cognitive impairment is indicative of potential benefits. This should stimulate further, larger-scale studies.

Declaration of interest
None.

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Lithium has been a subject reported on in this *Journal* for a very long time.[1] Perhaps unsurprisingly, in more recent decades most of the reports about the clinical use of salts of this monovalent cation have concerned its use as a treatment for affective disorders and despite its status as a generic medicine, new information about the benefits of lithium to health continues to be published. As consideration of these data has matured, early doubts about lithium's utility as a treatment[2] have been replaced by a solid and mature evidence base upon which we can confidently base clinical practice. A good example of this is the meta-analytic evidence which shows that the therapeutic use of lithium may prevent suicide.[3] Intriguing, though still not entirely conclusive, new evidence is published on this topic in the current issue.[4] For the treatment of bipolar disorder, lithium has good evidence for antimanic actions, although these benefits must be balanced against the likelihood of rebound mania upon stoppage.[5] The value of lithium, both as monotherapy and combined with valproate, for relapse prevention in bipolar disorder was also shown in the recent BALANCE study.[6] In contrast, lithium monotherapy performed disappointingly as an acute treatment for bipolar depression in a recent trial.[7] However, this lack of an antidepressant effect may possibly have been due to the relatively short-term (8 weeks) duration of this study. However, just when it seemed that knowledge of lithium and its benefits for neuropsychiatric disorders had reached an uncontroversial consensus, a twist in this tale has appeared. Studies, initially from the realm of affective disorders, produced new and, perhaps somewhat surprising, evidence that lithium may confer benefits in terms of preventing dementia.

Lithium, bipolar disorder and dementia

Nunes *et al*[8] compared the prevalence of Alzheimer's disease in 66 elderly euthymic patients with bipolar disorder who were on chronic lithium therapy with 48 similar patients who had not received lithium therapy recently. These case–control data suggested that lithium reduced the prevalence of Alzheimer's disease in patients with bipolar disorder to that found in the general elderly population. Nunes *et al*[8] discounted this effect of lithium as a result of a reduction in the number of affective episodes, as in their study this variable was equivalent between the lithium and non-lithium groups. They suggested rather that this putative effect of lithium was due to 'a result of its intrinsic biological effects in the brain' and speculated that the effect of lithium to inhibit the transcription of the glycogen synthetase kinase (GSK)-3 gene might be pivotal. Indeed, lithium had previously been shown to produce a relative inhibition of GSK-3-induced tau phosphorylation.[9] Subsequent studies confirmed that patients with affective disorders on long-term lithium had a reduced risk for Alzheimer's disease, albeit admitting that, because of the non-randomised nature of the data, these findings might be spurious.[10,11] Convincing proof of lithium's 'antidementia' properties would therefore require data from appropriately designed, prospective, randomised trials. A small, open-label study examined the effects of administering lithium carbonate to patients with Alzheimer's disease for up to 1 year.[12] Disappointingly, no cognitive benefits were found in the patients who completed the study. In a subsequent placebo-controlled, single-blind study, lithium sufate was used to treat patients with mild Alzheimer's disease for 10 weeks. Lithium treatment was not found to have significant benefits on either cognitive performance or on cerebrospinal fluid (CSF) concentrations of disease-related biomarkers.[13]

Thus, it might appear that lithium has joined the many compounds which, despite great promise at the earlier stages of evaluation, failed to show efficacy in clinical trials. However, two points are of note before we write lithium off on the basis of these data. First, these are only two small and preliminary trials. Larger trials, perhaps with different dosages of lithium for a different duration of time, may produce more positive results. Second, it may be inappropriate to test drugs in patients with fully manifest, albeit mild, Alzheimer's disease. Studies of patients at high risk may be more fruitful. Such an approach was taken by Forlenza *et al*,[14] members of the research group which had produced one of the original papers about the protective effects of lithium.[8] The main objective of this study was to assess the effect of long-term lithium treatment on the progression of cognitive deficits in patients with amnestic mild cognitive impairment (aMCI), a state which has a high rate of progression to frank Alzheimer's disease. In this study, the effect of lithium on CSF concentrations of putative Alzheimer's disease biomarkers was also measured. Forty-five individuals with aMCI were randomised to receive lithium (0.25–0.5 mmol/l) or placebo in a double-blind trial of 12 months duration. A significant decrease in CSF concentrations of phospho-tau and a better performance on cognitive measures was found in the lithium-treated group.

†See pp. 346–350, 351–356 and 406–407, this issue.

The number of patients who progressed from aMCI to Alzheimer's disease was higher in the placebo group (7 out of 20) than in the lithium treated group (4 out of 21), although this difference was not statistically significant. Clearly, this trial is encouraging and the effects of lithium on cognition and Alzheimer's disease biomarkers are very suggestive of likely benefit. The numbers progressing to Alzheimer's disease were lower, although albeit not significantly so, presumably because of the limited power of the study. This trial adds to the increasing evidence that lithium may have beneficial effects on the brain[15] and begs to be replicated in further randomised trials in patients with aMCI.

Where do we go from here?

Further trials will be required and these should incorporate the features of this study, which may have been related to its success. These include a long duration of treatment and a study of patients with aMCI rather than full-blown Alzheimer's disease. The dose of lithium used is also of note. We tend to assume that the lithium levels required for therapeutic effect are those derived from studies of mania.[16] In the present study, markedly lower levels were induced (0.25–0.5 mmol/l) for a much longer time period. The notion that lower levels of lithium for a longer period of time may have benefits for human health has received some recent support. In a study from Japan, Ohgami *et al*,[17] demonstrated that lithium levels in drinking water were significantly and negatively associated with suicide rates. These findings suggest that even very low levels of lithium in drinking water may play a role in reducing suicide risk within the general population. Such findings, when considered with the evidence from Forlanza *et al*[14] raise the possibility that environmental lithium may also prevent dementia and clearly suggest that epidemiological studies examining this should be carried out.

What about treatment?

The pharmaceutical industry is clearly very much focused on developing treatments for dementia, although results to date have been equivocal and no disease-modifying agents are either licensed or can be currently recommended for clinical use.[18] If such treatments were to be given to large numbers of at-risk individuals for prolonged periods of time, the commercial rewards to those owning the patents for such treatments are likely to be very considerable. Lithium of course is under no patent and will not attract industry funds for further development as a treatment except perhaps as a comparator to commercial compounds or possibly in combination with another agent. The onus is therefore on governmental and charitable funding agencies. Such trials will not be cheap, but were they to prove positive, the possible benefits in health to our ever-ageing population would be beyond any such price.

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References

1 Sainsbury H. Treatment of Insanity. *J Ment Sci* 1904; **50**: 565.

2 Moncrieff J. Lithium: evidence reconsidered. *Br J Psychiatry* 1997; **171**: 113–9.

3 Young AH, Hammond JM. Lithium in mood disorders: increasing evidence base, declining use? *Br J Psychiatry* 2007; **191**: 474–6.

4 Kapusta ND, Mossaheb N, Etzersdorfer E, Hlavin G, Thau K, Willeit M, et al. Lithium in drinking water and suicide mortality. *Br J Psychiatry* 2011; **198**: 346–350.

5 Goodwin GM. Recurrence of mania after lithium withdrawal. Implications for the use of lithium in the treatment of bipolar affective disorder. *Br J Psychiatry* 1994; **164**: 149–52.

6 Geddes JR, Goodwin GM, Rednell J, Azorin JM, Cipriani A. Ostacher MJ, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomized open-label trial. *Lancet* 2010; **375**: 385–95.

7 Young AH, McElroy SL, Bauer M, Philips N, Chang W, Olausson B, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry* 2010; **71**: 150–62.

8 Nunes PV, Forlenza OV, Gattaz WF. Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. *Br J Psychiatry* 2007; **190**: 359–60.

9 Lovestone S, Davis DR, Webster MT, Kaech S, Brion JP, Matus A, et al. Lithium reduces tau phosphorylation: effects in living cells and in neurons at therapeutic concentrations. *Biol Psychiatry* 1999; **45**: 995–1003.

10 Kessing LV, Sondergard L, Forman JL, Anderson PK. Lithium treatment and risk of dementia. *Arch Gen Psychiatry* 2008; **65**: 1331–5.

11 Kessing LV, Forman JL, Anderson PK. Does Lithium protect against dementia? *Bipolar Disord* 2010; **12**: 87–94.

12 Macdonald A, Briggs K, Poppe M, Higgins A, Velayudhan L, Lovestone S. A feasibility and tolerability study of lithium in Alzheimer's disease. *Int J Geriatr Psychiatry* 2008; **23**: 704–11.

13 Hamel H, Ewers M, Burger K, Annas P, Mortberg A, Bogstedt A, et al. Lithium trial in Alzheimer's disease: a randomized single-blind, placebo controlled, multicenter 10-week study. *J Clin Psychiatry* 2009; **70**: 922–31.

14 Forlenza OV, Diniz BS, Radanovic M, Santos FS, Talib LL, Gattaz WF. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. *Br J Psychiatry* 2011; **198**: 351–356.

15 Macritchie KAN, Lloyd AJ, Bastin ME, Vasudev K, Gallagher P, Eyre R, et al. White matter microstructural abnormalities in euthymic bipolar disorder. *Br J Psychiatry* 2010; **196**: 52–8.

16 Severus WE, Lipkovich LA, Licht RW, Young AH, Greil W, Ketter T, et al. In search of optimal lithium levels and olanzapine doses in the long-term treatment of bipolar I disorder. A post-hoc analysis of the maintenance study by Tohen et al 2005. *Eur Psychiatry* 2010; **25**: 443–9.

17 Ohgami H, Terao T, Shiotsuki I, Ishii N, Iwata N. Lithium Levels in drinking water and risk of suicide. *Br J Psychiatry* 2009; **194**: 464–5.

18 O'Brien JT, Burns A. Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. *J Psychopharmacol* 2010; Nov 18. Epub ahead of print.

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