BJPsych | The British Journal of Psychiatry (2017)
211, 1–2. doi: 10.1192/bjp.bp.116.193789

Editorial

# Recalibrating the risks and benefits of lithium therapy

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**Summary**
Recent data might subtly recalibrate the risk/benefit ratio of lithium, the prototypical mood stabiliser for bipolar disorder. There are hints that lithium might be associated with a reduction in dementia risk and as noted in this *Journal*, a surprising reduction in the risk of cancer.

**Declaration of interest**
M.B. reports grants from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier, Woolworths, Avant and the Harry Windsor Foundation, speaker support from Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay and Wyeth, and consultancies to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Eli Lilly, Grunbiotics, Glaxo SmithKline, Janssen Cilag, LivaNova, Lundbeck, Merck, Mylan, Otsuka, Pfizer and Servier.



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For more than 50 years lithium therapy has been the archetypal mood stabiliser for the treatment of bipolar affective disorders, and has been used as an adjunctive therapy in the management of unipolar depression. In practice, it has proven to be the most effective strategy for long-term prognosis in a significant proportion of patients with bipolar I disorder, especially those with a 'classic' manic–depressive pattern of illness, and is the only treatment shown to be effective in the prevention of suicide in affective disorders.[1,2] However, despite these important benefits, lithium therapy is perhaps more notorious for its long-term serious adverse effects – causing, in particular, appreciable thyroid and renal dysfunction.[3] For instance, long-term lithium therapy measurably diminishes the concentrating ability of the kidney in up to 40% of patients – making them prone to develop polyuria.[4] Therefore, the potential benefits and likely risks of treatment with lithium need to be carefully evaluated, especially since mood-stabilising therapy for bipolar I disorder is potentially lifelong. Indeed, this applies to all clinical decisions in medicine involving the institution of treatment that are predicated on achieving a fine balance between risks and benefits; but in the case of a medication such as lithium this ratio needs to be constantly reviewed as the risks tend to change with illness progression.

## Lithium therapy and cancer risk

Our understanding of the mechanisms of lithium action and its putative side-effects has recently increased and this too has shed light on recalibrating the effectiveness of lithium therapy. In this already complicated environment, an intriguing narrative has recently emerged concerning the possible relationship between lithium therapy and cancer. This discourse began with the fear that lithium might increase cancer risk and was initiated most likely by the probably erroneous observation of a 'cancer cluster' – the recognition of which has been subsequently criticised on the basis of methodological concerns.[4] Fortunately, this has launched a more systematic examination of the supposed relationship between lithium therapy and cancer risk. Although not all studies have shown a signal, a number of the more recent, suitably powered and methodologically rigorous investigations seem to be more definitive. In contrast to the initial report, these newer more robust studies found no association between the use of lithium and rates of either renal/upper urinary tract cancers or colorectal adenocarcinoma.[5,6] Indeed somewhat remarkably, some studies including one in this *Journal* suggest that lithium therapy is associated with a reduced risk of cancer.[7] For example, one nationwide study details an increased risk of respiratory, gastrointestinal and endocrine cancer in patients with bipolar disorder but only in those not on lithium therapy.[1]

A key question this raises is whether this is a real effect and if so how does lithium produce this effect? An extensive body of preclinical and clinical research has shown that lithium has a diverse range of effects that have an impact on targets within cell signalling pathways – some of which could explain its potential benefits in cancer. Specifically, it interacts with an enzyme, glycogen synthase kinase-3 (GSK-3), the actions of which are inhibited by lithium. GSK-3 is implicated in the pathogenesis of cancer, although its precise role is complex and the subject of much controversy.[8] This is not surprising given the multifaceted pathophysiology of bipolar disorder and the many actions of lithium on a multitude of pathways and systems – all of which remain to be fully elucidated.[7]

## Lithium therapy and dementia risk

In this context, the risks of lithium on renal and thyroid function are further offset by equally intriguing data on the relationship between lithium and the risk of dementia. Here again, there are compelling mechanistic hypotheses that suggest a potential avenue whereby lithium might reduce the risk of dementia. This is supported, in part, by the first generation of preclinical and



https://doi.org/10.1192/bjp.bp.116.193789 Published online by Cambridge University Press

epidemiological studies.[5] However, this substantial promise needs to be buttressed by confirmatory evidence. For instance, although recent data utilising 'micro-dose' lithium in mild cognitive impairment appears to confer possible benefits as a multitarget treatment in patients with dementia and Alzheimer's disease, further well-designed long-term trials are needed to confirm its safety and efficacy to examine whether long-term use of lithium achieves reasonable and sustained therapeutic benefit. Additionally, lithium may have neuroprotective potential in people receiving radiotherapy or chemotherapy.[8] This effect of lithium on cognition is complicated by the fact that at higher doses – those used for the treatment of bipolar disorder, for example – may appreciably compromise neurocognition, while simultaneously conferring some benefits; direct and indirect – putatively via mood mechanisms.[9]

## Implications for treating patients with bipolar disorder

If it is true that lithium might offer prophylactic capacity in both cancer and Alzheimer's disease – arguably two of the most important health challenges at a population level – then this has the capacity to meaningfully alter the current balance of the benefit–risk prescription equation. As a result of both the conflicting evidence base and the preclinical nature of the majority of current studies on lithium therapy, garnering a compelling evidence-base supporting or refuting lithium's properties in both cancer and dementia has become critical. With regard to the benefit side of the equation, there have been a number of recent reports suggesting lithium might be superior to other mood stabilisers in some circumstances. Observational data comparing quetiapine, valproate, olanzapine and lithium suggests benefits of lithium over the remainder in maintenance therapy and suicide risk.[10,11] If the promises postulated from the current studies are upheld, a compelling argument can be mounted for lithium to move even further up the priority rankings to first-line therapy. Intriguingly, and of some concern, despite the compelling evidence base for the primacy of lithium in bipolar disorder, the rates of lithium prescription are steadily declining. Thus, the recalibration of the risk/benefit ratio of lithium would hopefully go some way to redressing this problem and hopefully improve the prognosis for people with bipolar disorder who are lithium-responsive.

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First received 27 Oct 2016, final revision 12 Dec 2016, accepted 19 Dec 2016

## Funding

This project was supported by a grant from Astra Zeneca. M.B is supported by an NHMRC Senior Principal Research Fellowship (No. 1059660). L.W. is supported by an NHMRC Career Development Fellowship (GNT1064272).

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https://doi.org/10.1192/bjp.bp.116.193789 Published online by Cambridge University Press