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Lithium: balancing mental and renal health

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Dr Fransson and colleagues have undertaken an in-depth examination of kidney function in people treated with lithium in two large representative cohorts in Sweden.[1] Of over 2200 participants, the authors compared individuals with a bipolar/schizoaffective disorder with unaffected controls, finding that lithium is associated with steeper declines in estimated glomerular filtration rate (eGFR) and frequently is an attribution for chronic kidney disease (CKD). Firstly, they found a greater eGFR decline in patients than controls, with this difference seemingly explained by lithium use. Lithium use was reportedly associated with additional eGFR deterioration of 0.54ml/min/1.73m^2 per year treated (R^2=0.37). However, the effect of lithium on eGFR showed high inter-individual variation, and this pattern appears only significant for people taking lithium for $\geq$10 years. Of few CKD cases, 42% were definitively caused by lithium, with 25% partially attributable and 34% not attributable. Of the latter, half had not been exposed to lithium, and half of those exposed had lithium incorrectly recorded as CKD cause on medical records. Wrongful attribution of CKD as lithium-induced is concerning, as this appears to occur routinely, albeit infrequently.

The result about lithium exposure duration is important in helping to explain previously conflicting findings.[2] Altogether, caution is warranted around long-term lithium use at 'therapeutic' levels. However, regular monitoring can facilitate early detection and intervention of eGFR decline (for which progression tends to be gradual), to mitigate against permanent renal damage. This intervention may include treating comorbidities affecting renal function, as well as considering lithium discontinuation. The authors conclude that in these cases, a trade-off is needed between patients' mental health and their renal health, when considering whether lithium treatment should be sustained. This balance between benefits and harms should be prioritised in research as well as clinical practice.

Current priorities

These cautions do not preclude the use of long-term lithium as recommended in guidelines, given its effectiveness and safety for many[3], and the aforementioned ability for renal monitoring to circumvent CKD. In cases where lithium discontinuation is indicated, alternative effect mood stabilisers are available.[3] We instead advocate regular, careful eGFR monitoring adhering to guidelines.[3] We recommend large-scale audits and interventions to enhance monitoring. Research efforts can also focus on establishing risk profiles for future renal impairments.

What next for lithium?

Lithium's properties are well characterised, and its clinical benefits remarkable for their breadth. As well as being the gold standard mood stabiliser for bipolar disorders, lithium is effective in unipolar depression,[4] and evidence supports benefits related (but not limited) to suicidality,[5] neuroprotection and cognition.[6]

Interestingly, several strands of evidence are converging to suggest that substantially lower doses may confer benefits, with value evident even from environmental lithium exposure, whereby areas with higher lithium levels in tap water supplies appear to have reduced suicide[5] and dementia[7] rates (although whether these

findings can be extrapolated from a population- to individual-level remains unestablished). Trials of lithium for dementia/predementia suggest promising effects on cognition, with a meta-analysis suggesting comparable effects despite variable dose (range 300ug-168mg) across three studies.[6]

Can lithium be effective without incurring harms?

As well as lithium's potential to treat dementia (at low doses), there appears a clear case for low-dose lithium as a preventative intervention e.g., against cognitive decline[8] (suicide and mood disorders are other examples). Given its high (and increasing) burden, substantial public concern, clear risk factors and a recognised prodrome, effective preventative/early intervention strategies would have wide appeal. There are challenges with pharmacological and non-pharmacological prevention therapies, and 'natural' remedies can also have side effects and/or bioavailability issues. An optimal preventative treatment would be acceptable, effective, safe, accessible and scalable to a large at-risk population.

Some have turned to 'supplementary' lithium in very low doses. A 'microdose' of lithium orotate can be purchased without prescription as a nutritional supplement. Despite a distinct lack of human scientific studies, recent commentaries have extolled lithium orotate's potential:[9] Advocates highlight its use over several decades in the community without safety concerns, and safety is also supported by evidence from studies of low-dose lithium (other formulations),[10] and established knowledge of this mineral's pharmacodynamics. It has also been claimed that lithium orotate formulations impart benefits at lower doses than carbonate forms, and that the orotate anion itself could have biosynthetic advantages.[9]

The biological and clinical potential of trace (<~5mg/day) and micro (~5-20mg/day elemental lithium) doses require systematic investigation to verify the above claims in human studies. Prolonged exposure to low dose lithium could be one of several routes towards identifying how this environmental, bioavailable mineral could impart its magic effectively while averting chronic renal problems.

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Conflicts of interest

In the last 36 months, the following are declared.

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Both authors are employed by King's College London; AHY is an honorary consultant for South London & Maudsley NHS Trust. Both authors hold positions on journal editorial boards. Neither author declares shareholdings in pharmaceutical companies.

Author contributions

RS and AHY jointly conceptualised the content, wrote, reviewed, and approved the final manuscript. RS wrote the first draft of the manuscript.

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