

Lithium to Treat - Or Prevent - Dementia: A Short Discussion

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Abstract

Lithium is an agent with established neuroprotective qualities and considerable epidemiological evidence supporting its use as a dementia prophylactic. Yet it has failed to enter regular clinical use for this purpose-not for lack of evidence, but rather arguably for saturation of poor-quality evidence and aborted peripheral clinical trials. This narrative review discusses the story of lithium's almost rise to fame, and discusses future opportunities.

Keywords

Lithium, Dementia

Lithium

Since Soranus of Ephesus (circa 2nd century AD) prescribed salt baths from his hometown for patients suffering from mania [1] and its rediscovery by John Cade in the 1940s, lithium has had a central role in mental health, despite it being a mere salt, "just plain old lithium" [2]. As a multi-target drug, given activity in several intracellular cascades and oxidative stress pathways, it has been thought to have neuroprotective features and found to improve learning and memory in animal models [3]. In 2014, a systematic review of standard and trace-dose lithium identified 24 studies, within which 4 small randomized clinical trials of lithium found at least some clinical or biological benefits versus placebo, outside of control of bipolar disorder [4].

Controversially, even the coincidental finding of drinking water contamination with lithium has been found to be associated with a reduced incidence of dementia [3]. Notably, the mechanism for this last finding has been purported to be related to lithium's possible role in neuroprotection from lead exposure, given positive findings from animal studies that lithium pre-treatment mitigates lead toxicity [5]. This has not been a foregone conclusion- it must be noted that, whilst much of the enthusiasm for the use of lithium came from preclinical rodent studies, these have not translated well to patient populations- noting that there are several aspects of rodent brains different to those of humans.

More importantly, perhaps, as the authors of the study have noted, these differences relate to the issue that the animal studies started earlier in the disease process in those models than in the patient populations. In the studies which reported lower incidence of dementia in populations with higher lithium levels in their drinking water, there was likely a potential for lifelong exposure to lithium- which could be preventative.

This may be why it was in epidemiological studies that surprising coincidental benefits were discovered. A population-based cohort study [6] assessed

retrospectively over 40,000 people who had been diagnosed with bipolar disorder, to find that continued lithium use was associated with a reduced incidence in dementia diagnosis. A cohort of patients with no lithium exposure had an incidence rate of 2.45 (per 100 person-years), but with 301-365 days of exposure, this incidence rate dropped to 1.38. A Danish study found a reduction in dementia rate with continued prescription of lithium, although only to the same level as the rate of the general population [7].

A Targeted Mechanism of Action and Its (Apparent) Failure

Glycogen Synthase Kinase 3 (GSK3) inhibition was proposed as a mechanism for lithium's neuroprotective qualities, particularly its role as a regulator of amyloid precursor protein processing. According to the "GSK-3 hypothesis", over-activity of GSK3 accounts for memory impairment, tau hyper-phosphorylation, increased β -amyloid production and local plaque-associated microglial-mediated inflammatory responses [8]. Although the pathogenesis of Alzheimer's disease is recognized to be a process with multiple components, it was this unique property of lithium that was conceptualized to be a mechanism of disruption that could provide its neuroprotective effects. In the rat model, this was verified in multiple independent laboratories [9].

However, a 10 week randomized trial of lithium (0.5-0.8 mmol/L) in 71 patients with mild Alzheimer's disease did not show a change in CSF concentrations of GSK-3 activity, nor did it demonstrate a treatment effect in CSF-based biomarker concentrations of amyloid and precursors [10]. The authors considered this verified a failure of the hypothesis, but acknowledged the small sample size and the brief duration of the trial. As a further proof of concept assessment, the GSK3 inhibitor tideglusib was developed and investigated in a small number of patients with established Alzheimer's disease, to find no significant benefits on cognitive measures [11]. It was noted that this study primarily focused on safety and tolerability and the authors proposed a longer study was required to assess cognitive improvements [12].

These studies seem to suggest that the GSK-3 mechanism of purported neuro-protectiveness has been unsuccessful. However, these studies did not replicate positive findings from animal models in known established dementia- suggesting a limited role for lithium when dementia has already been confirmed. It is also notable that the animal studies prospectively assessed changes in amyloid accumulation from a much earlier stage than in human studies. Given what we know of the pathophysiology of Alzheimer's disease and the presence of amyloid well prior to observable clinical deficits [13], this suggests a reason for the unsuccessful trials. There are, of course, other possibilities- such as the relatively small number of study participants, and lithium's potential role (or lack thereof) in other forms of dementia.

However, apart from the issue of the apparent failure of this mechanism, there is the question of dose. A central issue of lithium has always been its difficulty of use in the

elderly, with a very narrow therapeutic index and propensity to inducing chronic renal impairment. It has been recognized that treating older people with traditional therapeutic daily doses (0.5 - 0.8 mmol/L) increases the risk of renal disease [3]. Aiming for these narrow margins, as a mechanism of long term prophylaxis, naturally leads to clinical trials with a high propensity for failure.

Disappointment, "The Bubble Pops"

Despite the aforementioned multifactorial apparent benefits, it was found to have no role in restoring cognitive function in established dementia [14]. Two randomized controlled trials in adults with mild to moderate Alzheimer's disease did not observe a protective lithium effect [9, 15], whereas another trial in participants with MCI but not yet manifest Alzheimer's disease found benefits in cognitive outcomes as well as biomarker outcomes [16].

The question of dose

A number of studies have dealt with the toxicity of lithium by considering low or very low dose lithium with surprisingly positive outcomes. Another mouse model study discovered that micro dose lithium (0.25 mg/Kg/day) led to a treated cohort with a decreased number of senile plaques, no neuronal loss in cortex and hippocampus and increased brain-derived neurotrophic factor density in the cortex, when compared to a non-treated cohort [17]. A small human study investigated the benefit of a daily dose of 300 ug lithium, to find significant protective benefit in mini-mental score performance 3 months after treatment [18]. One recalls the earlier-cited studies noting variations in cognitive protection associated with varying drinking water concentrations of lithium.

A randomized study [19] of 61 community-dwelling older adults with mild cognitive impairment found the lithium cohort had better performance in memory and attention after 24 months. Notably, this cohort received only low-dose lithium, at 0.25 - 0.5 mEq/L, approximately half standard doses.

To treat or to prevent

Recalling that animal studies appeared to center on disease progression when starting earlier in disease models, there appears to be much more of a focus on treating pre-established disease rather than in a primary prevention model. That is, the majority of studies are about lithium's potential role in treating dementia, rather than preventing it. This is particularly of relevance when one considers the drinking water contamination study and the possible mechanism of lifelong exposure [3].

With the benefit of hindsight, one can now consider a more nuanced approach to the use of lithium- as rather than a panacea for all cognitive issues, the question can be "What is the most logical/appropriate stage of disease development to target, and what dose and for how long to treat?" [12]- that is, to recognise that lithium has a higher likelihood of benefit in lower doses and in early or pre-Alzheimer's Disease states.

Opportunities for the future

Noting that its potential role in known bipolar disorder is already recognized, there are options to consider the use of lithium at low doses or trace doses, in groups with mild cognitive impairment- or perhaps even risk factors only. Could lithium be of benefit to a patient who is Apoe4 positive (and therefore prone to amyloid accumulation)? Or perhaps those who are positive for early amyloid presence as verified by PET imaging, but prior to clinical cognitive deterioration?

At time of writing there are 8 clinical trials registered with clinicaltrials.gov, all in varying states of progress, regarding the use of lithium in modified formats and with improving sophistication of target groups of intervention.

There are even potential options for reconsidering the formulation of lithium itself [20]. A novel micro dose formulation of lithium, coded NP03, was assessed in a rat study and found to address key components of Alzheimer's disease pathology (including GSK-3 inhibition and reducing amyloid levels, without significant renal impairment. The authors of the study state that this is related to the proprietary formulation minimising systemic circulation of lithium whilst maximising transmission across the blood-brain barrier. At time of writing human studies had not yet been trialled.

The remarkable possibility thus still remains, that an incurable disease with the largest burden currently facing medical science, may have a potential solution- nothing more than a simple salt.

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