Is there a miracle for dementia following bipolar disorder? Lithium and its neuroprotective effects

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The articles on lithium and Alzheimer's disease (AD) published in the August and September 2025 issues of Nature have generated significant attention in the neuroscience community. AD is the most common neurodegenerative pathology worldwide, leading to profound impairment in quality of life, health, and functioning, while reducing life expectancy, imposing a substantial economic and caregiving burden. Its multifactorial etiopathogenesis involves protein aggregation, mitochondrial dysfunction, oxidative stress, and neuroinflammation, all of which disrupt multiple cellular pathways, with effective treatment strategies still elusive. This makes the recent lithium–AD studies particularly noteworthy.

In these studies, spectrometric analyses revealed that among essential trace metals naturally present in brain tissue, only lithium was found to be significantly reduced in the prefrontal cortex of individuals diagnosed with Mild Cognitive Impairment (MCI) and AD compared to healthy controls (1). The same research group demonstrated in AD mouse models that dietary reduction of endogenous lithium by 50% accelerated cognitive decline through amyloid-β accumulation, tau hyperphosphorylation, pro-inflammatory microglial activation, and synaptic, axonal, and myelin loss. Interestingly, higher lithium concentrations were observed within amyloid plaques, suggesting that AD pathology may sequester lithium in affected regions, leading to depletion in other areas and thereby promoting disease progression. This raises the provocative question: Is AD, in part, a disorder of lithium deficiency? A disturbance in lithium homeostasis might contribute to the acceleration of pathology.

Some of lithium's restorative effects are mediated through inhibition of glycogen synthase kinase-3β (GSK3β) activity. Other proposed mechanisms include enhancing neuronal glucose uptake, promoting glycolysis to replenish ATP levels, upregulating the primary neuronal glucose transporter GLUT3, increasing glucose utilization in the hippocampus, and elevating glycolytic flux and the ATP:ADP ratio via AMP-activated protein kinase (AMPK) activation. Notably, mitochondrial dysfunction—long studied in bipolar disorder—has also been demonstrated in AD, suggesting another potential domain for lithium's therapeutic action.

In addition, lithium has been listed among candidate molecules (alongside rapamycin, mTORC1 inhibitors, metformin, clonidine, curcumin, nicotinamide, bexarotene, and trehalose) proposed to regulate autophagy, a pathway increasingly considered as a therapeutic target in AD.

According to the findings of Aron and colleagues, replacement therapy with lithium orotate in experimental mouse models reduced amyloid binding, prevented memory loss and pathological changes, and even reversed some neuropathological features. This critical outcome appears groundbreaking, as true reversal of pathology has not yet been achieved in dementia treatment.

DOI: 10.5505/kpd.2025.99885

Cite this article as: Cakir S. Is there a miracle for dementia following bipolar disorder? Lithium and its neuroprotective effects. Turkish J Clin Psych 2025; 28: 185-188

The arrival date of article: 18.09.2025, **Acceptance date publication:** 20.09.2025

Turkish J Clinical Psychiatry 2025;28:185-188

Lithium Orotate, Alzheimer's Disease, and Neuroprotection

Lithium orotate is a lithium salt with lower affinity for binding to amyloid plaques compared to lithium carbonate; paradoxically, it becomes more sequestered within plaques, thereby maintaining higher levels of lithium in brain tissue. Lithium orotate is administered at much lower doses than lithium carbonate and carries the additional advantage of minimizing metabolic side effects. However, as a relatively newer formulation, our knowledge regarding its pharmacokinetics, pharmacodynamics, toxicity thresholds, and therapeutic dose ranges in humans remains insufficient. Genetic and environmental factors may significantly influence lithium levels and could play an important role in explaining interindividual differences—an area warranting further investigation.

Among potential biomarkers for AD, brain lithium measurement holds promise for the future, though translational research is still required before it can be adopted in routine clinical practice. While there is currently no clinical trial evidence demonstrating the efficacy of lithium orotate in AD, it clearly represents an emerging and important field of investigation.

As with most neuropsychiatric disorders, reducing the AD–lithium relationship to one or two mechanisms is unlikely to capture the complexity of brain pathologies with intricate network interactions, especially given the role of gene–environment interactions in disease etiopathogenesis. The emerging discussion of metal homeostasis, including lithium, thus represents an important conceptual advance in AD research (2). Another intriguing finding regarding lithium orotate relates to amyloid plaques being negatively charged: these may attract and sequester positively charged lithium ions, thereby depleting intracellular lithium. Lithium orotate, by contrast, is not ionized, which enables it to bypass this "trap," restore neuronal function, and contribute to healthier, "younger" brain physiology with improved cognitive outcomes (3).

It is worth recalling the earlier studies—possibly an inspiration for the current research groups—that examined trace levels of lithium in municipal drinking water in relation to dementia prevalence. These studies largely investigated the effects of naturally occurring lithium concentrations (μg/L) in water supplies on long-term dementia risk. A nationwide Danish cohort study spanning 1970–2013, which included 73,731 dementia patients and 733,653 controls, found lower lithium exposure among dementia patients (4). While long-term higher lithium exposure appeared to reduce the risk of dementia (particularly AD and vascular dementia), the potential confounding effects of socioeconomic status, nutrition, and genetics could not be excluded. Another study demonstrated that water lithium levels ranging from 0.002 to 0.056 mg/L were associated with lower AD mortality and reduced prevalence of obesity and type 2 diabetes—both known risk factors for AD—whereas levels below 0.002 mg/L were ineffective (5). In contrast, negative studies reporting no association between water lithium and dementia typically involved substantially lower lithium levels (6, 7). Taken together, these findings suggest that adequate long-term lithium exposure through drinking water (>10–15 μg/L) may reduce dementia incidence and AD mortality. Moreover, one study demonstrated that the protective association of water lithium against AD was more pronounced in women, pointing to the need for further research on the interplay of lithium, AD, gender, and hormonal factors (8).

This raises another critical question: in bipolar disorder, where lithium is most widely used, is there a difference in AD risk between patients who do and do not receive lithium treatment? How effectively does lithium preserve cognitive function in this population? Despite some negative findings, the potential protective role of lithium in reducing dementia risk has become increasingly prominent. While bipolar disorder itself, along with multiple associated factors, increases dementia risk, lithium use appears to mitigate this risk (9). Notably, long-term continuous use provides neuroprotective benefits through mechanisms such as GSK3β inhibition and anti-inflammatory effects, whereas short-term or intermittent use does not. Compared to alternative mood stabilizers such as valproate, lithium appears more advantageous in preserving cog-

nitive reserve (10).

Thus, the molecule discovered in 1949 for its antimanic properties—later established as the gold-standard maintenance treatment in bipolar disorder, and the only pharmacologic agent proven to reduce suicide rates—now emerges after 76 years in psychiatry as a potentially transformative intervention in AD and neuropsychiatry, through mechanisms yet to be fully elucidated. For clinicians, the challenge and responsibility lie in using this molecule in appropriate indications while skillfully managing side effects, thereby maximizing its potential to deliver profound therapeutic benefits in select patients.

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