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Review Article

A Review on Role of Lithium in Alzheimers Disease

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Abstract

Alzheimer's disease (AD) is characterised by amyloid accumulation, tau hyperphosphorylation, and progressive cognitive decline. Emerging evidence suggests that lithium, even at trace levels, supports neuronal survival by modulating GSK-3β, enhancing neurogenesis, reducing inflammation, and stabilising mitochondria. Epidemiological and experimental studies indicate that lithium deficiency may increase AD risk, while microdose lithium shows promise in improving cognition and reducing pathology with minimal toxicity. This review summarises current findings linking lithium deficiency to AD and highlights its potential as a preventive neuroprotective strategy.

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1. INTRODUCTION

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative condition marked by memory loss, cognitive impairment, and characteristic brain changes such as amyloid plaques and neurofibrillary tangles.[1] It represents the most common cause of dementia globally, responsible for 60–70% of cases.[2] Its core pathological processes involve extracellular accumulation of amyloid-β (Aβ) and intracellular buildup of hyperphosphorylated tau, both of which disrupt synaptic communication and neuronal function.[3] These abnormalities trigger a series of damaging events, including neuroinflammation, oxidative stress, mitochondrial failure, and eventual neuronal degeneration.[4] Although significant research has been dedicated to understanding AD, currently approved

treatments mainly target symptoms and do not stop or reverse the underlying disease.[5]

Lithium, a monovalent cation long used as a mood stabiliser in bipolar disorder, has recently been recognised for its potential neuroprotective actions.[6] Evidence indicates that even very low or trace levels of lithium can influence neuronal signalling pathways relevant to neurodegeneration.[7] Mechanistic studies show that lithium inhibits glycogen synthase kinase-3β (GSK-3β), an enzyme central to tau hyperphosphorylation and amyloid precursor protein (APP) dysregulation, two major contributors to AD pathology.[8] Lithium also modulates Wnt/β-catenin signalling, increases neurotrophic factors like BDNF, and enhances synaptic plasticity, thereby promoting neuronal health.[9] Additionally, lithium reduces oxidative stress and neuroinflammation by suppressing microglial activation and supporting mitochondrial function.[10]

Growing evidence suggests that insufficient lithium exposure, either dietary or environmental, may elevate the risk of cognitive decline and dementia.[11] Ecological studies from multiple countries have reported inverse associations between lithium levels in drinking water and rates of AD. [12] Experimental research further confirms that lithium deprivation accelerates amyloid buildup, inflammation, and neuronal loss, resembling AD-like changes. [13] Conversely, low-dose lithium supplementation has been shown to reduce amyloid and tau pathology and improve cognition in both animal models and early human trials.[14]

Altogether, these findings indicate that lithium may have an essential neuroprotective role even at trace concentrations, and that inadequate lithium exposure may contribute to AD pathogenesis. This review synthesises available evidence on how lithium deficiency relates to AD, focusing on molecular pathways, epidemiological data, and therapeutic significance.[15]

Physiological Role of Lithium in the Brain

Lithium is a naturally present trace mineral involved in maintaining normal brain signalling and cellular activity.[16] Although not officially classified as an essential nutrient, increasing evidence suggests that physiological lithium levels support key neuroprotective and neuromodulatory processes.[17] In the brain, lithium influences several intracellular pathways—such as the phosphoinositide cascade, cyclic AMP regulation, and Wnt/β-catenin signalling—that jointly regulate synaptic plasticity and neuronal survival.[18] It also affects enzymes, including GSK-3β and inositol monophosphatase, both critical for gene expression, neuroplasticity, and energy metabolism.[19] Lithium supports mitochondrial health by enhancing the efficiency of the electron transport chain and reducing the production of reactive oxygen species.[20] It also contributes to calcium balance, protecting neurons from excitotoxicity and apoptosis.[21] Lithium helps regulate neurotransmitter systems, including serotonin, dopamine, and glutamate, which are essential for mood regulation and cognitive function.[22] Moreover, it promotes the expression of neurotrophic molecules such as BDNF and NGF, aiding neuronal repair, growth, and synaptic remodelling.[23]

Evidence from both animals and humans suggests that long-term lithium deficiency may weaken these protective mechanisms, increasing susceptibility to mood disorders, cognitive decline, and neurodegeneration.[24] Experimental models show that inadequate lithium disrupts neurotrophic signalling, enhances inflammation, and contributes to neuronal death in memory-related brain regions.[25] Observational data in humans indicate that populations exposed to low-lithium drinking water exhibit higher rates of affective disorders and possibly dementia, emphasising lithium's importance for brain health.[26]

Concept of Lithium Deficiency

Lithium deficiency refers to inadequate intake or environmental exposure to lithium, resulting in levels too low to support optimal brain function.[27] Though not officially designated as an essential element, research increasingly suggests that lithium may behave as a conditionally essential micronutrient due to its influence on behaviour, metabolism, and neural signalling.[28] Lithium content in food and water varies widely across geographic regions depending on soil minerals, climate, and geological factors, producing significant differences in population exposure.[29] Regions with very low groundwater lithium levels have shown increased rates of depression, suicide, and cognitive issues, suggesting that chronic deficiency may heighten neuropsychiatric risks.[30]

Epidemiological studies consistently show higher rates of mood disorders and dementia in communities with low environmental lithium exposure.[31] In contrast, moderate trace levels of lithium in drinking water correlate with reduced suicide rates and slower cognitive decline.[32] This suggests a dose–response pattern in which both insufficient and excessive lithium may be harmful.[33] Lithium deficiency is thought to alter cellular pathways such as GSK-3β, inositol monophosphatase, and Wnt signalling, thereby impairing neuroplasticity and cellular resilience.[34]

Measuring lithium deficiency remains difficult, as no universal biomarker or recommended reference range exists.[35] Current approaches include assessing lithium in serum, urine, CSF, hair, nails, or brain tissue.[36] However, these samples may not reliably represent long-term levels or regional brain distribution.[37] Modern techniques such as ICP-MS and laser ablation spectroscopy have improved detection accuracy for trace lithium.[38]

Despite expanding interest, lithium deficiency is not yet a formally recognised clinical diagnosis, and no dietary guidelines exist.[39] Some researchers suggest that chronic intake under ~0.1 mg/day may represent inadequate exposure, though this is still under debate.[40] Animal studies indicate that lithium deprivation leads to memory deficits, oxidative stress, and AD-like tau and amyloid pathology, supporting the concept of biologically meaningful deficiency.[41] Overall, current evidence highlights lithium's overlooked but potentially crucial role in maintaining neurological stability, suggesting that deficiency may be a modifiable risk factor for neurodegenerative and mood disorders.[42]

Epidemiological Evidence Linking Lithium and Alzheimer's Disease

Epidemiological research increasingly demonstrates a protective association between low-dose lithium exposure and decreased Alzheimer's disease risk.[43] Large ecological studies show that regions with higher natural lithium in drinking water have lower AD incidence and mortality.[44] A major Danish study involving over 800,000 people reported an inverse relationship between tap-water lithium levels and dementia risk, even at very low concentrations.[45] Similarly, Japanese nationwide analyses found that areas with more lithium in water supplies had reduced AD-related mortality and slower cognitive decline.[46] Studies from Brazil also reported similar patterns, suggesting worldwide relevance.[47]

Clinical and cohort studies support these findings. Patients with AD often exhibit reduced lithium levels in serum and cerebrospinal fluid compared to healthy controls.[48] Postmortem research further confirms decreased lithium concentrations in the hippocampus and cortex of AD brains.[49] Long-term population studies show that individuals chronically exposed to trace lithium display slower cognitive ageing and reduced dementia onset.[50] Clinical trials examining microdose lithium supplementation (0.3–1 mg/day) show promising outcomes.[51] A 15-month randomised trial found that microdose lithium stabilised MMSE scores and reduced CSF phosphorylated tau in individuals with early AD.[52] Long-term follow-up studies further showed maintained cognitive benefits for up to three years.[53] However, limitations include small sample sizes and inconsistent exposure histories.[54]

Collectively, these data suggest that adequate exposure to trace lithium may protect against AD.[55] But differences in study methodology, exposure measurement, and regional variability make direct comparisons difficult, underscoring the need for standardised research approaches.[56] Lithium thus appears to be a potentially modifiable environmental factor influencing dementia risk globally.[57]

Experimental and Preclinical Evidence

Preclinical research provides strong support for lithium's neuroprotective effects in AD. Animal models demonstrate that lithium-deficient diets accelerate plaque buildup and cognitive decline, while supplementation improves learning and reduces pathology in transgenic mice.[58] Laboratory studies reveal that lithium influences APP processing, reduces $A\beta_{1-42}$ formation, and limits plaque accumulation through modulation of key signalling pathways.[59] Lithium's inhibition of GSK-3β is central to these effects, reducing tau hyperphosphorylation and stabilising microtubules.[60] Early mechanistic studies showed that lithium enhances microtubule assembly and reduces tau toxicity.[61]

Lithium also promotes neurogenesis, especially in the hippocampus. Human progenitor cell studies show increased cell proliferation and differentiation with lithium treatment.[62] Preclinical analyses additionally highlight lithium's capacity to reduce oxidative stress and neuroinflammation.[63] A 2025 Nature study provided compelling evidence that lithium deficiency is strongly linked to AD pathology, showing dramatically reduced brain lithium levels in MCI and AD patients. Restoring physiological lithium levels in mice reversed memory deficits and reduced Aβ and phosphorylated tau.[64] Parallel microdose trials in humans report slowed cognitive decline versus placebo, though larger trials are still required to validate these findings.[65]

Mechanistic Insights

Lithium deficiency disrupts multiple biological pathways that accelerate AD pathology.[66] One major mechanism is the loss of GSK-3β inhibition, which normally helps regulate tau phosphorylation and APP processing.[68] Reduced lithium increases GSK-3β activity, leading to excessive tau phosphorylation, microtubule breakdown, and enhanced amyloid deposition.[69] Lithium deficiency also impairs hippocampal neurogenesis, reducing neuronal renewal and weakening memory-related structures.[70] At the cellular level, insufficient lithium contributes to mitochondrial dysfunction, elevated oxidative stress, and increased apoptosis.[71] It also intensifies neuroinflammation by activating microglia and promoting cytokine release.[72] Lithium regulates Aβ metabolism, and low levels impair peptide clearance, increasing plaque buildup.[67] Additionally, lithium modulates neurotransmitter systems; deficiency disrupts glutamate and dopamine signalling, worsening cognitive and behavioural symptoms.[73]

Therapeutic Implications

Low-dose or microdose lithium has emerged as a potential preventive or disease-modifying therapy for AD.[74] Unlike standard psychiatric doses, trace-level lithium provides neuroprotection without significant toxicity.[75] Animal studies show that dietary low-dose lithium reverses amyloid and tau pathology and restores cognition in lithium-deficient or AD-model mice.[76,77] Microdose lithium primarily works through GSK-3β inhibition, reducing tau pathology and affecting APP processing.[78] It also enhances neurogenesis, stabilises mitochondria, and reduces inflammation.[79]

Clinical trials support these findings: patients with MCI receiving microdose lithium show slower cognitive decline than placebo groups.[80] Epidemiological data also suggest population-wide benefits where water contains trace lithium.[81] Some public health proposals suggest supplementing water or diets with trace lithium, though ethical and safety considerations remain.[82] Determining effective dosing, identifying biomarkers, and conducting large-scale trials are critical future steps.[83]

Safety and Toxicity Considerations

While therapeutic lithium doses can cause renal, thyroid, or neurological side effects, microdose or trace levels appear safe for long-term use.[84] Levels below 0.3 mEq/L generally do not produce the adverse effects associated with psychiatric dosing.[85] Animal studies confirm that microdose lithium provides neuroprotection without systemic toxicity.[86] Human

trials also show that long-term low-dose lithium does not significantly affect renal or thyroid function, even in older adults.[87]

However, more research is needed to identify the lowest effective concentration for neuroprotection and to establish monitoring strategies for safe use.[88]

Knowledge Gaps and Future Directions

Despite substantial progress, several gaps remain in understanding lithium's role in AD.[89] Optimal lithium concentrations for cognitive protection are still unclear.[90] No validated biomarker exists for assessing deficiency or treatment response.[91] Large, long-term randomised studies are needed to establish causality between lithium and reduced AD risk. [92]

Future studies should integrate advanced tools such as 7Li-MRI, CSF biomarkers, and genetic profiling to clarify lithium's effects in the human brain.[93] Such approaches may enable personalised lithium-based strategies for neuroprotection. Ultimately, robust clinical trials are needed to establish guidelines for safe and effective lithium supplementation in AD prevention and treatment.[94]

CONCLUSION

Lithium deficiency may contribute to AD pathology by disturbing essential signalling pathways and reducing neuronal stability. Trace or microdose lithium shows neuroprotective effects in preclinical and early clinical studies, indicating possible benefits in slowing cognitive decline. Larger, rigorous trials are required to determine ideal dosing, identify biomarkers, and confirm long-term safety for its preventive or therapeutic use in AD.

REFERENCES

1. Alzheimer's Association. 2025 Alzheimer's disease facts and figures. *Alzheimer's Dement*. 2025.
2. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. *Lancet*. 2021;397(10284):1577–1590.
3. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med*. 2016;8(6):595–608.
4. Heneka MT, Golenbock DT, Latz E. Neuroinflammation in Alzheimer's disease. *Lancet Neurol*. 2015;14(4):388–405.
5. Cummings J, Lee G, Nahed P, et al. Drug development in Alzheimer's disease: the path to 2025. *Alzheimer's Res Ther*. 2022;14(1):113.
6. Forlenza OV, Diniz BS, Teixeira AL. Neuroprotective effects of lithium: implications for Alzheimer's disease. *ACS Chem Neurosci*. 2014;5(6):443–450.
7. Mauer S, Vergne D, Ghaemi SN. Lithium: pharmacodynamic actions of a fascinating drug. *Ther Adv Psychopharmacol*. 2014;4(2):75–87.
8. Phiel CJ, Wilson CA, Lee VM, Klein PS. GSK-3α regulates amyloid-β production. *Nature*. 2003;423:435–439.
9. Chiu CT, Chuang DM. Molecular actions and therapeutic potential of lithium in neurodegenerative diseases. *Pharmacol Ther*. 2010;128(2):281–304.
10. Machado-Vieira R, Manji HK, Zarate CA. Lithium modulation of neurotrophic and inflammatory pathways. *Mol Psychiatry*. 2020;25:2213–2224.
11. Fajardo VA, McMeekin L, LeBlanc PJ. Lithium deficiency as a risk factor for Alzheimer's disease. *Nutrients*. 2022;14(18):3756.
12. Ishii N, Terao T, Araki Y, et al. Lithium in drinking water and dementia mortality: a meta-analysis. *Int J Environ Res Public Health*. 2021;18(8):4212.
13. Aron L, et al. Lithium deficiency induces Alzheimer-like pathology. *Nature*. 2025.
14. Forlenza OV, et al. Low-dose lithium for Alzheimer's disease: a randomised trial. *Br J Psychiatry*. 2019;215(4):668–674.
15. Shen Y, et al. Molecular mechanisms and therapeutic potential of lithium in Alzheimer's disease. *Front Pharmacol*. 2024;15:1345.
16. Schrauzer GN. Lithium: occurrence, dietary intakes, nutritional essentiality. *J Am Coll Nutr*. 2002;21(1):14–21.
17. Szklarska D, Rzymski P. Is lithium a micronutrient? *Biol Trace Elem Res*. 2019;189(1):18–27.
18. Klein PS, Melton DA. Molecular mechanism of lithium action. *Proc Natl Acad Sci U S A*. 1996;93(16):8455–8459.
19. Berridge MJ, Downes CP, Hanley MR. Neural and developmental actions of lithium. *Cell*. 1989;59(3):411–420.
20. Quiroz JA, et al. Mitochondrial dysfunction and lithium neuroprotection. *Bipolar Disord*. 2010;12(3):274–282.
21. Malhi GS, Tanious M, Das P. The science and practice of lithium therapy. *Aust N Z J Psychiatry*. 2012;46(3):192–211.
22. Memon A, Rogers I, Fitzsimmons S. Geographical variation in lithium and mental health. *Environ Geochem Health*. 2020;42(7):2291–2312.
23. Kapusta ND, et al. Lithium in drinking water and suicide mortality. *Br J Psychiatry*. 2011;198(5):346–350.
24. Helbich M, et al. Lithium in drinking water, Alzheimer's disease mortality, and suicide. *JAMA Psychiatry*. 2022;79(4):388–395.
25. Viana da Silva S, et al. Trace lithium and human health. *Sci Total Environ*. 2023;873:162328.
26. Barceloux DG. Lithium toxicity. *J Toxicol Clin Toxicol*. 1999;37(2):293–308.
27. Schrauzer GN, Shrestha KP. Lithium in drinking water and crime/suicide incidence. *Biol Trace Elem Res*. 1990;25(2):105–113.
28. Aihara K, et al. Lithium levels in tap water and suicide in Japan. *Int J Environ Res Public Health*. 2021;18:7926.
29. Lim J, et al. Trace lithium quantification using ICP-MS. *Anal Bioanal Chem*. 2023;415(10):2251–2263.
30. Kessing LV, et al. Lithium in drinking water and dementia incidence. *JAMA Psychiatry*. 2017;74(10):1005–1010.

31. Giacobini E, Pepeu G. Lithium and dementia prevention. *Neurobiol Ageing*. 2020;94:157–166.
32. Nunes MA, et al. Microdose lithium in Alzheimer's disease. *Curr Alzheimer Res*. 2013;33:893–901.
33. Matsunaga S, et al. Lithium for Alzheimer's disease: a systematic review. *J Alzheimers Dis*. 2023;95(2):395–410.
34. Bauer M, et al. Ethical considerations of trace lithium supplementation. *Front Psychiatry*. 2023.
35. Hampel H, et al. Designing lithium prevention trials for Alzheimer's disease. *Alzheimer's Dement*. 2024.
36. Gitlin M. Lithium side effects and toxicity. *Int J Bipolar Disord*. 2016.
37. O'Donnell T, et al. ^{7}Li-MRI imaging of lithium distribution in the brain. *Neuroimage*. 2022.
38. Andreazza AC, et al. Genomic and mitochondrial biomarkers of lithium response. *Mol Psychiatry*. 2024.

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