

Low-Dose Lithium for Cognitive Decline: What the Evidence Actually Shows

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The question is whether lithium, a drug most clinicians associate with bipolar disorder and narrow therapeutic windows, has a second career as a neuroprotective agent at doses far below those used in psychiatry. Epidemiological signals have kept this hypothesis alive for over a decade, and small trials have followed; the immediate takeaway is that the evidence is not yet strong enough to change prescribing practice, but it is substantial enough that dismissing the question entirely would be premature.

KEY TAKEAWAYS

- **The Pivot:** Low-dose lithium (doses as low as 150–300 mg daily, targeting serum levels well below the 0.6–1.2 mmol/L therapeutic range for bipolar disorder) has been investigated specifically for cognitive preservation in mild cognitive impairment and early Alzheimer's disease, separate from its psychiatric indications.
- **The Data:** Randomised trial data in this space remain limited to small studies; the largest published RCT in mild cognitive impairment enrolled fewer than 100 participants, limiting any conclusions about effect size with confidence.
- **The Action:** Do not initiate lithium for cognitive preservation outside a clinical trial context; monitor this space as larger adequately powered RCTs are ongoing, and counsel patients asking about this that the evidence base does not yet support routine use.

Lithium's potential as a neuroprotective compound rests on a plausible biological rationale. At the cellular level, lithium inhibits glycogen synthase kinase-3 beta (GSK-3beta), an enzyme implicated in tau hyperphosphorylation, and has been shown in preclinical models to reduce amyloid-beta production and promote neurotrophic signalling via brain-derived neurotrophic factor (BDNF).¹ These are not trivial pathways: GSK-3beta inhibition addresses one of the central molecular lesions in Alzheimer's disease pathology, and the fact that lithium engages it at low serum concentrations made the low-dose hypothesis scientifically credible rather than speculative.¹

The epidemiological data added weight. Population-level analyses of patients prescribed lithium for psychiatric indications over many years observed lower-than-expected rates of dementia diagnosis in that cohort compared with matched controls not on lithium.² Ecological studies examining lithium concentrations in drinking water found inverse associations between naturally occurring lithium levels and dementia mortality rates at a population level.² Neither category of evidence establishes causation, and confounding in both directions is substantial, but the signal was consistent enough to justify prospective investigation. The consistency across different epidemiological methodologies, despite their inherent limitations in controlling for all potential confounders, suggested a biological effect warranting further

investigation in controlled clinical settings. For instance, individuals receiving lithium for bipolar disorder often have extensive medical comorbidities and receive other psychotropic medications, making direct comparisons challenging. Conversely, ecological studies cannot account for individual-level risk factors for dementia. However, the repeated observation of a protective association across these diverse datasets provided a compelling impetus for clinical trials.

What the trials have actually shown

The clinical trial programme in this area is best characterised as early-phase and underpowered rather than definitive. The most cited randomised controlled trial, conducted by Forlenza and colleagues in Brazil, enrolled 41 participants with amnesic mild cognitive impairment and randomised them to lithium carbonate at a dose targeting serum levels of 0.25 - 0.5 mmol/L or placebo over 12 months.³ The lithium group showed statistically lower cerebrospinal fluid phosphorylated tau concentrations at 12 months compared with placebo, and performed better on one cognitive subscale (the ADAS-Cog delayed recall), though cognitive outcomes were secondary endpoints and the trial was not powered to detect clinical progression to dementia.³ A later open-label extension suggested the effect on biomarkers persisted, but open-label data carry obvious limitations.³ The selection of amnesic mild cognitive impairment (aMCI) as the target population in this trial was strategic, as aMCI is often considered a prodromal stage of Alzheimer's disease, offering a window for potential disease modification before extensive neurodegeneration occurs. The specific dose range chosen aimed to achieve serum levels significantly lower than those used in psychiatric practice (typically 0.6-1.2 mmol/L), thereby mitigating the risk of common lithium-related adverse effects while still potentially engaging the desired neurobiological pathways. The primary outcome focused on a biomarker of Alzheimer's pathology, phosphorylated tau, reflecting the mechanistic hypothesis that lithium could directly impact disease progression at a molecular level.

A separate randomised trial, the IGLiAD study, examined microdose lithium (300 micrograms daily, substantially below even the low-dose definition used by Forlenza et al.) in patients with Alzheimer's disease and reported stability on the Neuropsychiatric Inventory compared with placebo at 15 months, but again the sample was small and the primary endpoint was not cognitive decline per se.⁴ The tolerability profile at these doses appeared comparable to placebo, which matters clinically: the principal concern with lithium at therapeutic levels, namely renal impairment, thyroid dysfunction, and the narrow therapeutic index requiring monitoring, is substantially attenuated at sub-therapeutic doses, though not absent.⁴ The IGLiAD study's focus on neuropsychiatric symptoms, rather than cognitive decline, highlights another facet of Alzheimer's disease management where lithium might offer benefit, given its established mood-stabilizing properties. However, the extremely low dose used raises questions about its ability to exert significant neuroprotective effects through the same mechanisms as higher, albeit still low, doses. The small sample sizes across these initial trials are a consistent limitation, restricting the generalizability of their findings and increasing the risk of both type I and type II errors.

What the trial programme does not yet have is a large, adequately powered, phase III randomised trial with dementia incidence as the primary endpoint and a follow-up period of at least three to five years. Without that, the biomarker data, while mechanistically coherent, cannot be translated into a prescribing recommendation. Biomarker surrogacy in Alzheimer's disease has a poor track record of predicting clinical benefit, as the amyloid immunotherapy field has demonstrated at considerable cost.¹ The ongoing LATTICE trial and similar initiatives represent the next necessary step, but results are not yet available in the public domain.⁵ The design of such a definitive trial would need to address several critical factors, including patient selection (e.g., individuals with early Alzheimer's disease, prodromal AD, or even at-risk asymptomatic individuals), optimal dosing strategy, and the duration of treatment required to observe a

meaningful clinical effect on dementia progression. Furthermore, the logistical challenges of conducting long-term trials in neurodegenerative diseases, including patient retention and consistent monitoring, are substantial. Until such robust evidence emerges, the use of low-dose lithium for cognitive decline remains an investigational approach, not a clinical standard.

CLINICAL IMPLICATIONS

The most striking consequence of where this evidence currently sits is that patients are almost certainly ahead of their clinicians on this one. Low-dose lithium for dementia prevention is discussed extensively in longevity and healthy-ageing communities, and GPs are already fielding requests from cognitively intact patients in their fifties who want to start it prophylactically. The honest answer to those patients is that no trial has yet enrolled cognitively normal adults as a prevention population, that the longest randomised follow-up in any relevant trial is under two years, and that prescribing outside a trial in this context means accepting personal liability for an off-label intervention whose long-term renal and thyroid effects at low doses have not been characterised in large cohorts. That is not a comfortable conversation, but it is the accurate one.

The pharmaceutical industry has been conspicuously absent from this research programme, and the reason is straightforward: lithium is off-patent, cheap, and therefore offers no commercial return on a phase III investment. The trials that exist have been investigator-initiated and publicly funded, which is also why they are small. If the LATTICE trial or a comparable adequately powered study produces a positive result, the beneficiaries will not be a named manufacturer but generic lithium suppliers, and the National Institute for Health and Care Excellence (NICE) or equivalent bodies will face the unusual problem of evaluating a prevention indication for a decades-old molecule with no industry-sponsored dossier. Guideline infrastructure is not well designed for that scenario.

For the moment, the clinical action is containment rather than adoption. Lithium at low doses is not ready for routine cognitive preservation use, and clinicians who are tempted by the biological plausibility should weigh the absence of incidence data against the real, if attenuated, monitoring burden the drug still carries. That said, patients enrolled in properly constituted trials should be encouraged to participate: this question will not answer itself, and the only path to a verdict is through adequately powered prospective data that the field does not yet have.

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