

Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Lithium

Evidence Summary

Small clinical trials suggest potential disease stabilization, but data are mixed. Lithium has serious safety concerns. Lower dose or novel formulations are under investigation, but efficacy is not yet known.

Neuroprotective Benefit: Small clinical trials have reported mixed results for use of lithium in dementia; the longer studies suggest disease stabilization. Epidemiological studies also are conflicting but may hint at benefit. More robust studies are needed.

Aging and related health concerns: There is some preclinical evidence suggesting potential benefit for health conditions such as stroke, but clinical evidence is lacking.

Safety: Lithium requires titration to the therapeutic range. Severe lithium toxicity can risk coma or even death. Therapeutic doses can lead to GI side effects, weight gain, tremor, and affect renal and thyroid function. Monitoring and low doses can mitigate risks.

Availability: By prescription (higher dose), in diet, or as an over-the-counter supplement (lower dose).	Dose: For psychiatric patients, dose is titrated to achieve desired serum levels approximately between 0.4 and 1.2 mmol/L, depending on the patient characteristics or stage of treatment (e.g. acute stabilization vs. maintenance). Doses typically range between 900 and 1800 mg daily, orally. Achieving the proper dose is extremely important.	Chemical formula: Li MW: 7 g/mol 3 Li Lithium 6.941 Source: PubChem
Half-life: 18 to 36 hours	BBB: Penetrant.	
Clinical trials: Lithium has been tested in numerous clinical trials for different indications over decades. Some of the largest meta-analyses for lithium treatment include over 1,000 patients.	Observational studies: Lithium has been examined in many observational studies and it is thought that hundreds of thousands of patients take lithium each year. The largest study identified in this report included over 40,000 patients, 6,900 of whom had taken lithium.	

What is it?

Lithium is a chemical element and is used for a variety of applications, including as medicine. Lithium compounds such as lithium carbonate, the most widely prescribed formulation, have been widely used for decades as both an acute and chronic treatment for major psychiatric disorders ([Alda et al., 2015](#); [Hampel et al., 2019](#); [Hamstra et al., 2023](#)). Lithium is a first-line treatment for mood stabilization; it is approved for use in bipolar I disorder and is prescribed for managing manic and mixed episodes. It is also prescribed off-label as an adjunct therapy for major depression, for bipolar disorder without history of mania, vascular headaches, and neutropenia ([Chokhawala et al., 2024](#)). Lithium is also thought to have specific anti-suicide effects ([Alda et al., 2015](#)). Upon ingestion, lithium spreads throughout the central nervous system, and can result in mood stabilization – typically on the order of 1 to 3 weeks, though this can vary ([Chokhawala et al., 2024](#)). The exact mechanism of action is not clear, although

lithium can modulate many aspects of cellular function in the brain, including neuronal excitability, regulation of neurotransmission, mitochondrial function, and oxidative stress through effects on different proteins and cell signaling cascades ([Malhi et al., 2013](#); [Alda et al., 2015](#); [Hampel et al., 2019](#)). It may be that lithium acts through multiple mechanisms, potentially depending on dose.

Lithium has a narrow therapeutic range and has very significant potential adverse events, leading to a black box warning for lithium toxicity. Lithium toxicity can occur at doses close to therapeutic range. Any use of prescription doses of lithium should be accompanied by regular blood monitoring when individuals start treatment or experience side effects. Monitoring recommendations vary, but many clinical practice guidelines recommend blood level monitoring approximately a week after treatment initiation and after dose increases ([Nolan et al., 2019](#)), as well as regular monitoring of approximately 2 to 4 times per year during maintenance treatment ([Nederlof et al., 2018](#)). The timeline of monitoring may depend on patient characteristics.

A note on nomenclature of units: for lithium, mEq/L is equivalent to mmol/L. This report will use these units based on the reference publication, but they can be read interchangeably.

Neuroprotective Benefit: Small clinical trials have reported mixed results for use of lithium in dementia; the longer studies suggest disease stabilization. Epidemiological studies also are conflicting but may hint at benefit. More robust studies are needed.

Types of evidence:

- 13 meta-analyses or systematic reviews
- 18 clinical trials
- 14 observational studies
- 10 reviews
- 1 press release of a clinical trial
- 3 commentary letters on a clinical trial
- Numerous preclinical studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Lithium is a first line treatment for bipolar disorder, and bipolar disorder is thought to increase risk of dementia. A number of meta-analyses and/or systematic reviews, clinical trials, and observational studies have investigated the impacts of lithium on cognition or incidence of dementia in both psychiatric and non-psychiatric populations. Some of these meta-analyses have assessed data from studies of patients with MCI or AD. The meta-analyses and the studies they assess will be discussed in the 'Human research to suggest benefits to patients with dementia' section, as the majority of the included studies focus on patients with dementia.

It is not known whether a protective effect of lithium in populations of psychiatric patients would translate to lower dementia incidence for other populations. Given the association between bipolar disorder and dementia, it is unclear whether lithium provides cognitive benefit or is instead reducing a risk through treating the underlying mood disorder. It is also possible that lithium treatment is merely correlated with a decreased risk that is in fact mediated through another mechanism, such as the fact that lithium treatment implies the patient is receiving medical care, or if lithium treatment is preferentially given to healthier patients. These observational studies have other technical limitations, such as relying on lithium prescriptions rather than monitoring blood levels of lithium and the clinical heterogeneity of the patient populations who receive lithium prescriptions ([Huang et al., 2024](#)). While one can address some of these limitations, such as by comparing patients who received lithium to those who received other medications for bipolar disorder as [Gerhard et al., 2015](#) did, it remains a caveat for these kinds of studies.

A 2025 systematic review included any interventional trial of lithium. Their review included 30 studies of a total of 727 participants. Of these 30 studies, 13 included patients with affective disorders, 11 included patients with neurocognitive disease including AD and HIV-associated neurocognitive disorder, and 6 studies included healthy individuals. The researchers report significant heterogeneity in study design and results, precluding meta-analysis. Overall, approximately a third of the studies that assessed global cognition and memory reported significant improvements in these domains, with the remaining two-thirds showing either non-significant changes, decline, or mixed findings. Significant improvements in domains of processing and psychomotor speed, attention, and verbal fluency and executive function were reported by 25% or fewer studies that tested these domains ([Sabtari et al., 2025](#)).

Lithium aspartate, a lithium formulation that is sold as a supplement, has been tested in a double-blinded RCT for neurologic post-COVID-19 condition, also known as long COVID. The researchers ran this trial after anecdotal feedback from several of their patients that lithium aspartate relieved fatigue and cognitive dysfunction within days of starting the supplement, along with lithium's potential for anti-

inflammatory mechanism of action. The study randomized 52 patients with long COVID to receive either lithium aspartate capsules or matching placebo for 3 weeks. The lithium capsules contained 5 mg elemental lithium each, and patients were instructed to take 2 per day for the first 10 days with the potential for dose escalation to 3 pills per day for the next and last 11 days of the trial if they did not experience symptomatic relief. At the end of the 3 weeks of dosing, patients could continue to an open-label extension for an additional 2 weeks at the same dose. Of the 52 patients who started the study, 45 completed the RCT phase and open-label extension. There were no significant differences between the groups in the primary outcome of self-reported fatigue or brain fog symptoms, nor any other outcome measure ([Guttuso et al., 2024](#)).

After the end of the open-label extension, one patient purchased lithium aspartate and reported to investigators that a dose of 45 mg/day provided symptomatic relief. The researchers then initiated a dose-finding study. They invited open-label extension completers who were not placebo responders to enroll. Patients were told to take 10 mg per day of lithium aspartate and increase by 5 mg every week to a maximum of 45 mg per day, as tolerated. Of the 43 patients invited to this portion of the study, 5 enrolled. In this very small sample, one withdrew due to adverse events and no perceived improvement, two patients reported no improvement, and two patients reported subjective improvements. The two participants who reported improvements had higher serum levels of lithium (0.18 and 0.49 mEq/L) compared to those who reported no improvement (0.1 and <0.1 mEq/L) ([Guttuso et al., 2024](#)). These sample sizes are much too small to draw any conclusion but may provide an illustrative example for the range of serum lithium concentrations that can be observed from doses of supplemental lithium.

Other studies have examined the impact of lithium on cognitive function and/or incidence of dementia in patients with psychiatric diagnoses who received lithium as a psychiatric treatment. While a full exploration of the impacts of lithium on cognitive function of patients with psychiatric disorders is outside the scope of this report, a meta-analysis and systematic review published in December 2025 examined the data from RCTs on the effect of lithium on cognitive function in patients with bipolar disorder. The study included 9 RCTs comprised of 570 patients. The researchers caution that their results are preliminary. They found that in adolescents, lithium treatment significantly improved accuracy of emotional processing (SMD=-1.18; 95% CI -1.69 to -0.67, $p<0.00001$) and prolonged reaction time of emotional processing (SMD=-0.39; 95% CI -0.73 to -0.05, $p=0.02$). Treatment with lithium was not associated with significant changes in attention or working memory in adolescents or overall cognitive function in adults ([Qi et al., 2025](#)).

The effects of lithium on cognition have been tested in a few other populations, including postoperative patients and patients with multiple sclerosis (MS), though these studies do not offer definitive findings. [NCT05126238](#) was an RCT exploring whether lithium decreased surgical morbidity such as postoperative delirium or agitation in patients receiving carotid artery surgery. According to their [clinicaltrials.gov](#) record, the study was prematurely terminated due to the decision of the local ethics committee after enrolling 107 of the planned 500 patients; no further details on the termination decision were found. [Rinker et al., 2020](#) describes a small 2-year crossover study of lithium in 23 patients with primary or secondary progressive MS. Patients were randomized to one of two groups: one received lithium in year 1 and then placebo in year 2, and the other group received placebo in year 1 and lithium in year two. When participants were in the lithium phase of the study, they received 150 or 300 mg of lithium daily, depending on tolerance. This crossover design enabled the researchers to compare an individual patient on or off treatment, while also allowing the study team to be blinded to what a given patient was receiving at any given assessment. Patients were unblinded to their assignment for the given year. There were no differences in patients on or off lithium, though some participants did complain of cognitive slowing at higher doses.

Observational studies have explored the association between lithium prescription and incidence of dementia. Some studies such as [Chen et al., 2022](#), [Nunes et al., 2007](#), [Kessing et al., 2010](#), and [Gerhard et al., 2015](#) have reported that lithium use is associated with a lower incidence of dementia and reduced measures of brain aging (reviewed in [Sajatovic et al., 2013](#)). However, other studies like [Dunn et al., 2005](#) and [Ponzer et al., 2023](#) found no association between lithium treatment and dementia incidence.

Subsequent systematic reviews and meta-analyses have similarly reported conflicting findings. [Parlapani et al., 2026](#) performed a systematic review of 9 studies of older patients (mean age ≥ 50 years) with bipolar disorder and looked at the association between lithium use and dementia incidence. They found that compared to non-users, lithium use was associated with lower incidence of dementia in 6 of the 9 studies, neither higher nor lower incidence in 2 of the studies, and 1 study reported a higher incidence of dementia in lithium users compared to non-users.

[Huang et al., 2024](#) performed a systematic review and meta-analysis of observational studies that assessed the association between use of lithium and major neurocognitive disorders (e.g. AD) in patients with psychiatric disorders or the general population. In the eight included studies comprising 377,060 participants, the researchers found that there was no association between lithium use vs. non-use in terms of incidence of dementia (OR=0.94; 95% CI 0.77 to 1.24) or AD (OR=0.69; 95% CI 0.31 to 1.65); the

results were similarly non-significant when they restricted their analysis to studies of individuals with bipolar disorder. Subgroup analyses indicated that lithium was associated with a lower incidence of dementia in studies graded as low-quality, but there were no significant associations in studies graded as high-quality studies. They found high heterogeneity in their results, citing this as the most important limitation. [Lu et al., 2024](#), published shortly before the meta-analysis by Huang and colleagues, similarly performed a meta-analysis assessing the association between lithium and incidence of dementia. This meta-analysis included 7 studies and did find that lithium use was associated with a lower incidence of AD (RR=0.59; 95% CI 0.44 to 0.78) and dementia (RR=0.66, 95% CI 0.56 to 0.77).

Other papers have been published since these systematic reviews and/or meta-analyses. [Deonarine et al., 2026](#) performed a retrospective cohort study in adults 50 years or older with bipolar disorder or recurrent major depressive disorder. Patients who had documentation of lithium exposure for at least 1 year were propensity-score matched 1:1 to patients who had not used lithium and followed for a maximum of 5 years. The groups each included 67,020 patients. The researchers reported that use of lithium was associated with a lower incidence of AD (RR=0.49; 95% CI 0.33 to 0.74). The authors caveat that their study had a low event rate, with an AD diagnosis in 34 patients in the lithium group and 69 patients in the non-user group.

A not-yet peer reviewed paper by [Weckstein et al., 2026](#) reports on a new-user, active comparator target trial emulation that assessed progression of AD and related dementias in ≥55-year-old patients with bipolar disorder and mild neurocognitive disorders after initiating either lithium or antiepileptic mood stabilizers. The target trial emulation used data from US Medicare Claims, with 1,044 lithium users and 8,331 antiepileptic mood stabilizer users in their comparison groups after statistical adjustment for potential confounders. Replication analyses were performed with data from two other medical claims databases. In their primary sample, they reported that lithium-initiators had a lower incidence of progression to advanced dementia in 5 years than those who initiated antiepileptic mood stabilizers (RR=0.87; 95% CI 0.78 to 0.99). The replication analyses in the other two databases yielded similar findings (RR= 0.90; 95% CI 0.68 to 1.14 and RR=0.57; 95% CI 0.30 to 0.90). This study has the limitations inherent to a preprint, as well as to an observational study that cannot completely rule out residual biases, such as the possibility that lithium is prescribed more often to medically healthier individuals.

Observational studies of individuals with bipolar disorder are subject to limitations as discussed briefly in the introduction to this section of the report.

Epidemiological work also hints at a protective effect of non-pharmaceutical lithium against dementia, though the findings are not without controversy. Lithium is a natural element and can be found in rocks, soil, and ground water in varying concentrations in different geographic regions. Several studies have investigated whether there are any associations between lithium concentration in drinking water and neurological conditions. It should be noted that mental health diagnosis rates can also vary significantly based on regional resource availability and demographics, and there are other confounding factors when comparing geographic region and incidence of diagnosis that make these epidemiological studies challenging to run and interpret.

[Fraiha-Pegado et al., 2024](#) performed a systematic review of 5 studies investigating associations between lithium levels in drinking water and either incidence of or mortality from dementia. They reported that 4 of the 5 studies found significant associations between higher levels of lithium and lower incidence of dementia or lower mortality from dementia when they did not control for confounders. The one study that did not find an association was based in Scotland and also reported one of the lowest levels of lithium ([Duthie et al., 2023](#)). Once the studies controlled for confounders, one found an association between higher lithium and lower incidence of dementia in men and women ([Kessing et al., 2017](#)), and another found a lower incidence just in women ([Muronaga et al., 2022](#)). [Parker et al., 2018](#) reported no significant association between groundwater lithium levels and incidence of dementia or bipolar disorder after they adjusted for demographics and health care resources in the United States. [Fajarado et al., 2018](#) reported an association between drinking water lithium levels and a lower incidence of mortality from AD; this association was statistically significant after adjusting for several factors such as sex, education, rural living, and air pollution, but statistical significance was lost after adjusting for inactivity, type 2 diabetes, and type 2 diabetes + obesity. Fraiha-Pegado and colleagues conclude that the more comprehensive studies with lower potential for bias reported an association between higher lithium and lower incidence of dementia.

[Hwang et al., 2026](#) was published after the above systematic review. This study, assessing county-level associations between drinking water lithium and incidence of dementia, covered most of the United States. The researchers found a lower incidence of dementia in counties with higher concentrations of lithium compared to lower concentrations of lithium. Curiously, they found that all-cause mortality in patients with dementia was higher in counties with higher levels of lithium in drinking water, though this was attenuated after stratification by county-level Hispanic population percentage.

Controversy also exists over whether increased groundwater lithium levels are associated with decreased incidence of suicide or not ([Eyre-Watt et al., 2021](#)).

Human research to suggest benefits to patients with dementia:

Four total meta-analyses and/or systematic reviews have assessed the impact of lithium on cognition in patients with MCI, AD, or other dementia. These meta-analyses largely include the same studies. The results of each meta-analysis will be discussed, followed by a table of the studies in MCI and AD to date and more in-depth descriptions of the studies.

[Kishi et al., 2026](#) performed a random-effects meta-analysis of 6 total studies of patients with MCI or AD with a total of 435 patients ([Hampel et al., 2009](#), [Forlenza et al., 2011](#), [Nunes et al., 2013](#), [Devanand et al., 2022](#), Matsunaga [unpublished], [Gildengers et al., 2026](#)). The authors cite several limitations of the meta-analysis, including the small sample sizes, lack of biomarker characterization in all but one study, the grouping of MCI with AD, and the inclusion of an unpublished study in their analysis. The meta-analysis indicated that there was no significant difference in cognition between the group treated with lithium and the placebo group ($p=0.14$), with low or very low confidence in the evidence given the variety of limitations of the included studies.

[Pereira da Silva et al., 2026](#) included 6 publications with 394 patients in their systematic review and meta-analysis of lithium in patients with MCI or AD ([Hampel et al., 2009](#), [Straten et al., 2011](#), [Forlenza et al., 2011](#), [Forlenza et al., 2019](#), [Nunes et al., 2013](#), [Devanand et al., 2022](#)). The pooled analysis showed that there was no consistent significant difference in cognitive function, neuropsychiatric symptoms, or biomarker changes between patients treated with lithium compared to placebo. The researchers state that due to the heterogeneity observed in the results, as well as methodological limitations of the included studies, definitive conclusions cannot be drawn.

[Singulani et al., 2024](#) performed a systematic review and meta-analysis of preclinical and clinical studies assessing the impact of lithium in AD as well as in Parkinson's disease (PD). They reviewed three clinical studies ([Nunes et al., 2013](#), [Devanand et al., 2022](#), and [Forlenza et al., 2019](#)). Ultimately, the small number of studies precluded meta-analysis, but the authors report that all three studies reported a cognitive or non-cognitive benefit of lithium compared to placebo. It should be noted that some of these differences were in exploratory outcomes after null findings for the primary and secondary outcomes.

A 2015 systematic review and meta-analysis assessed the efficacy of lithium on cognitive function in patients with MCI or AD. The work included a total of 232 patients in 3 randomized placebo-controlled studies ([Hampel et al., 2009](#), [Forlenza et al., 2011](#), [Nunes et al., 2013](#)). The meta-analysis showed that the patients who received lithium had significantly less impairment than those who received placebo as measured by standard mean difference (SMD) (SMD=-0.41; 95% CI -0.81 to 0.02, p=0.04). When they separated MCI from AD, they found that the effects were not significant in MCI (p=0.59) but showed a statistical trend in AD (p=0.07). They did not find any significant difference in changes in AD relevant biomarkers (total tau, phosphorylated tau, or A β -42). The authors also reported that the study from Nunes and colleagues had the most statistically significant results.

The table below summarizes the studies in MCI and AD populations with cognitive outcomes. Note that maintenance therapeutic concentrations are generally 0.6 to 0.8 mEq/L, with option for decrease down to 0.4 or up to 1.2 mEq/L based on the patient characteristics and response ([Nolen et al., 2019](#)). The studies are described in greater detail after the table.

Study	Population + Design	N	Dose / Target Serum Concentration + Reported Serum Concentration if Included	Outcome(s) + Caveats
Macdonald et al., 2008	Mild to moderate probable AD, open label for up to 1 year	22	100 mg per day; target 0.2 to 0.8 mmol/L	No significant differences
Hampel et al., 2009 ; biomarker substudy in Straten et al., 2011	Mild probable AD, single blind for patients 10-week RCT	71	Target 0.5 to 0.8 mmol Li	No significant differences
Forlenza et al., 2011 , Aprahamian et al., 2014 ; Forlenza et al., 2014 , Forlenza et al., 2019	MCI, 2-year blinded RCT followed by 2-year single blind for investigators	61	Target 0.25 to 0.5 mEq/L; mean 0.4 mEq	Significant disease stabilization in treated patients vs. placebo. Note: placebo group significantly older than lithium group.
Nunes et al., 2013	Probable AD, 15-month RCT	113	300 μ g per day	Significant disease stabilization in



				treated patients vs. placebo
Devanand et al., 2022	Possible or probable AD, 12-week RCT	77	Target 0.20 to 0.60 mmol/L	No significant difference between groups on primary or secondary outcome measures.
Matsunaga et al., 2025*	Mild to moderate probable AD, 52-week RCT	46	300 µg per day	No significant differences between groups
Gildengers et al., 2026	MCI, 2-year RCT	88	150 mg or 300 mg per day, titrated to maximum tolerated dose	No significant differences between groups

* This trial is unpublished and thus not peer reviewed; the data was available through a clinical trial registry and meta-analyzed in Kishi et al., 2026

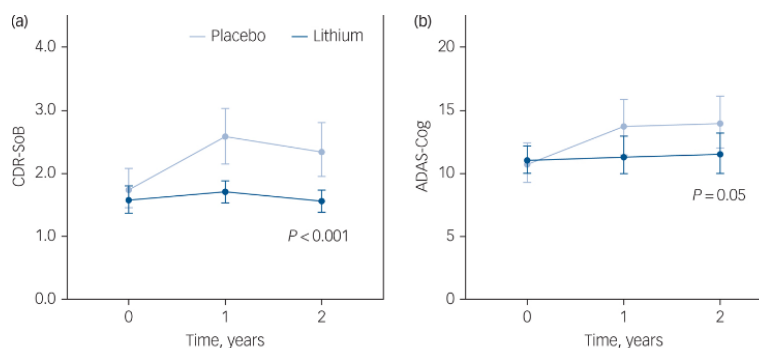
The trial described by [Forlenza et al., 2011](#) was a randomized controlled clinical trial in patients with MCI testing low-dose lithium or placebo for up to four years. The findings were published in multiple papers. The trial enrolled 61 physically healthy participants with MCI. In the first two years, the study was double-blinded; in the second two years, the participants were unblinded so that they could decide whether to proceed with treatment, but investigators remained blinded. Participants receiving lithium were given doses to achieve blood concentrations of 0.25 to 0.5 mEq/L. One note on this study is that at baseline, the placebo group was significantly older than the lithium treated group (mean age 74.8 vs. 71.6 years, respectively).

In their first paper detailing the results of 45 participants in the first year of treatment, lithium appeared to reduce tau phosphorylation and potentially mitigated cognitive decline ([Forlenza et al., 2011](#)). Subsequent publications raised some concerns, including both potential long-term safety risks and decreased metabolism in the brain and hippocampus, possibly suggesting lithium toxicity to the very areas of the brain that are most at risk of Alzheimer's disease ([Aprahamian et al., 2014](#); [Forlenza et al., 2014](#)). In 2019, the group published the results of the primary and secondary outcomes in the full sample after the entire follow-up period ([Forlenza et al., 2019](#)). In the final sample, the lithium treated group was still significantly ($p=0.03$) younger than placebo group; the average age in the lithium group was 71.2 (standard deviation [SD]=5.4) and in placebo group it was 74.4 (SD=6.1). There were no other noted baseline differences, including no significant differences in levels of CSF A β , total tau, or

phosphorylated tau. The average serum level of lithium was 0.39 mEq/L in the double-blind phase, and 0.41 mEq/L in the extension phase.

Overall, the researchers found that patients in the lithium group were largely cognitively and functionally stable over the course of the 2-year double-blind period, while the placebo group had mild decline that was significantly greater than the lithium group. However, the magnitude of difference was small. The table below includes the change from baseline scores on the ADAS-COG and CDR-SB for the lithium and placebo groups. The possibility that the older age of the placebo group contributed to this difference in scores cannot be ruled out.

Assessment	Lithium, mean (SD)	Placebo, mean (SD)	<i>P</i>
CDR-SB	-0.22 (0.9)	0.53 (1.8)	<0.05
ADAS-COG	0.83 (1.1)	1.8 (1.9)	<0.05



Linear mixed model (type III test of fixed effects) addressing the interaction between treatment group, time of intervention, and group x time for lithium and placebo treatment after 1 and 2 years of the double-blinded phase of the trial on the a) CDR-SB and b) ADAS-COG ([Forlenza et al., 2019](#)).

The researchers also assessed conversion from MCI to dementia. In the lithium group, 5 (16%) patients converted, whereas 9 (30%) of the placebo group did; this result was not statistically significant ($p=0.06$). The study also reported that between 12 and 36 months, the lithium group showed an increase in CSF levels of A β , largely driven by those with higher CSF A β at baseline; the authors speculated that this could potentially reflect A β clearance. There were no reported changes in tau or phosphorylated tau; the preliminary results reported in [Forlenza et al., 2011](#) were ultimately not borne out in the full study size or timeframe. In 2023, the group published another paper after reaching out to their original participants for follow-up information and inviting them to participate in a recall study. This recall study was 11 to 15 years after the end of the RCT and open-label extension period. Of the original 61 participants, they were able to collect data on 36, 22 of whom received lithium and 14 of whom

received placebo; 11 of the 36 patients, split evenly between the groups, were deceased and the researchers spoke to their caregiver. At this timepoint, there was no longer a statistical difference in age between groups. The researchers report that the patients who were assigned to the lithium group had significantly higher MMSE scores than those assigned to the placebo group (25.5 SD, 5.3 vs. 18.3 SD, 10.9, $p=0.04$), respectively. This was in a small sample size of 25 patients, and the researchers performed several other statistical associations; it is not clear whether there was any correction for multiple comparison. There was no statistical difference in the percentage of each group that had a dementia diagnosis or were deceased ([Damiano et al., 2023](#)).

A 15-month study of 113 patients with AD randomized patients to either a microdose of lithium (300 μg) or placebo, and the only outcome measure was cognitive function as assessed by MMSE. Participants were established patients and thus had cognitive testing as measured by MMSE once every 6 months in the year before the trial. During the trial, they were assessed by MMSE once every three months. The patients had relatively similar MMSE scores and trends before the trial began. During the trial, the treated group's MMSE scores stayed stable, whereas the placebo group's MMSE scores significantly declined in comparison (Friedman test, $p<0.001$) ([Nunes et al., 2013](#)).

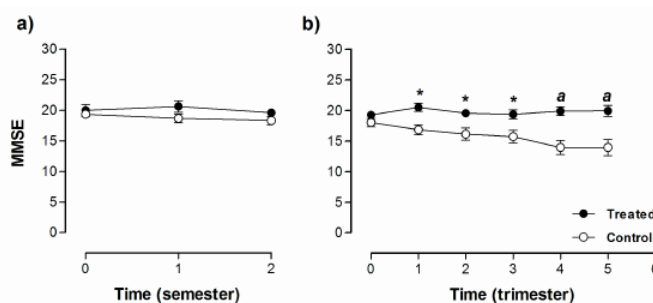


Fig. (1). Scores in the mini-mental state examination (MMSE) of subjects from control or treated groups before placebo or lithium therapy (a) and after the beginning of the therapy (b). The "Semester" 2 in panel "a" corresponds to "Trimester" 0 in panel "b". Data are expressed as means $\pm$ S.E.M. Statistical differences are represented by * ($P < 0.01$) and α ($P < 0.001$).

Other studies have not replicated these results but have their own caveats. [Hampel et al., 2009](#) describes a randomized controlled trial of 71 participants with mild AD randomized to either placebo or lithium treatment with a target serum level of 0.5 to 0.8 mmol/L lithium. The trial lasted for 10 weeks, consisting of a 6-week titration period followed by a 4-week maintenance phase. The trial was single-blind; participants were not aware of their assignment, but investigators were not blinded. The primary outcome measures were levels of CSF phosphorylated tau and GSK3 activity in blood. Secondary outcome measures included CSF levels of total tau, A β , and cognitive assessments including ADAS-COG and MMSE. There were no statistically significant differences between groups on any measures, though

there was a non-significant trend ($p=0.11$) towards cognitive benefit of lithium, with 28% of lithium-treated patients vs 15% of controls exhibiting a clinically significant improvement in their cognitive scores ([Hampel et al., 2009](#)).

[Macdonald et al., 2008](#) reports on a small open-label study of 22 patients with mild to moderate AD for up to 1 year. Patients were started at a dose of 100 mg daily and titrated to a steady state of between 0.3 and 0.8 mmol/L lithium. While there was no placebo group, the authors compared the participants in this trial to matching participants in another ongoing trial of AD patients; the patients in both studies had been recruited through the same process and had very similar clinical assessments. Only 8 patients completed the trial. There were two deaths, neither thought to be related to lithium treatment. The other 12 patients discontinued for a variety of reasons; 3 were due to apparent side effects, the others due to other illness, consent withdrawal, inability of care home to guarantee correct dosage administration, or other non-lithium-related reason. There was no difference in deaths, discontinuations, or change in cognitive score between the lithium treated group and the comparison group; however, the already small study became very small by the end of treatment.

[Gildengers et al., 2026](#) details a double-blind RCT known as LATTICE. The trial enrolled 83 patients 60 years or older with MCI. Participants were randomized to receive 150 mg or 300 mg of either lithium or matching placebo daily or every other day for 2 years. The exact timing was based on each participants' medical status and other medications, and dose was adjusted to the maximum tolerated dose. The mean dose was 195 mg of lithium with a mean serum level of 0.17 mEq/L. While the study did not require amyloid-positive PET scans, most participants received one scan and randomization was stratified based on presence of A β plaques. Approximately 25% of both groups were A β +. There was no statistically significant difference between groups on any of the 6 coprimary outcomes of the study, which included 3 cognitive assessments, 2 neuroimaging measures, and 1 assessment of BDNF levels as a biomarker measure. The lithium group had a trend towards mitigated decline in verbal memory ($p=0.05$), though this did not reach the pre-specified threshold for statistical significance of $p<0.01$. Exploratory analyses suggested that there may be a larger effect of lithium in A β + participants, but the sample size of these analyses was small.

The other two studies included in at least some of the above meta-analyses and/or systematic reviews are [Straten et al., 2011](#), [Devanand et al., 2022](#), and unpublished data from Matsunaga and colleagues. [Straten et al., 2011](#) describes a substudy of participants in the study by [Hampel et al., 2009](#). The study by [Devanand et al., 2022](#) primarily looked at the effects of lithium on agitation. Some of the exploratory efficacy and safety outcomes included measures of cognitive function such as MMSE. There was very

little information on the trial from Matsunaga and colleagues beyond the trial description in the table above.

A 2024 systematic review and meta-analysis assessed the comparative efficacy, tolerability, and acceptability of lithium and three anti-amyloid therapies: donanemab, lecanemab, and aducanumab in patients with MCI and AD. The analysis included 89 patients from two studies on lithium, both described above: [Nunes et al., 2013](#) and [Forlenza et al., 2019](#). The authors report mixed results: that lithium was significantly more effective than the three anti-amyloid drugs when looking at changes on MMSE; that all four drugs outperformed placebo but were not significantly different from one another on ADAS-COG; and that lithium was not significantly better than placebo on CDR-SB whereas donanemab and lecanemab both performed better than placebo. Whether these results speak to perhaps different benefits of the drugs (e.g. on functional performance vs. memory) or speak only to the very small size of the lithium trials and the preliminary results thereof is not yet known ([Terao & Kodama, 2024](#)).

Lithium has also been tested in different formulations and in different neurodegenerative diseases. [NCT05423522](#) was an RCT in patients with AD that tested nanolithium (NP03), a microdose of lithium that is encapsulated and administered buccally, allowing for very low dose lithium to be given. The study randomized 72 participants to receive buccal doses of 3 mL (1.8 mg) lithium or matching placebo once daily. There was a 12-week double-blinded phase followed by an optional open-label extension for 36 weeks. The primary outcome was change in neuropsychiatric symptoms. According to [Alzforum](#), a press release from the drug maker Medesis Pharma announced that while the patients treated with lithium trended towards improvement on the primary outcome, the difference between groups was not statistically significant. No further details on the results were found.

Trials of lithium in ALS have found no benefit of lithium in this population, as [Gamez et al., 2013](#) reports in their meta-analysis of more than 1,100 patients with ALS. [NCT06008249](#) was an RCT of lithium (target concentration 0.4 and 0.8 mmol/L) in a specific subgroup of ALS patients who have a specific polymorphism in the *UNC13A* gene. The study was terminated early after a planned interim analysis showed no survival benefit of lithium compared to placebo. A small RCT tested whether lithium showed any sign of efficacy for agitation and motor behavior in 16 patients with FTD but there was no difference between the placebo and lithium group at the end of the trial ([Zide et al., 2025](#)). Lithium has also been tested in a very small open-label pilot study of 16 patients with PD. Participants received one of three doses of lithium: a 'high-dose' of lithium carbonate to achieve a blood level of 0.4 to 0.5 mmol/L, a 'medium dose' of 45 mg/day of lithium aspartate, or a 'low dose' of 15 mg/day of lithium aspartate. The study primarily assessed biomarkers but the small sample sizes make it challenging to assess the results. It is worth noting that 2 of the 6 patients randomized to receive the medium dose withdrew from the

study due to 'sedation, incoordination, and slowness of thinking', though no other patients reported any side effects ([Guttuso et al., 2023](#)).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Lithium can affect a dizzying array of cellular activities, many of which may have benefits for neurological health; it is therefore not clear which mechanism(s) may mediate neuroprotection. Some of the most prominent current theories focus on the neuromodulatory actions of lithium.

One of the most prominent and best supported mechanistic theories of the neuromodulatory action of lithium—specifically in the context of AD and other related dementias—is via lithium's inhibitory effects on glycogen synthase kinase 3 (GSK3) ([Noble et al., 2005](#); [Engel et al., 2008](#); [Chiu & Chuang, 2011](#); [Wilson et al., 2017](#); [Snitow et al., 2021](#); [Chatterjee & Beaulieu, 2022](#); [Ruiz & Eldar-Finkelman, 2022](#)).

There are two very similar isoforms of GSK3: GSK3 α and GSK3 β . Unless otherwise specified, GSK3 will refer to both enzymes. GSK3 has over 100 targets and is involved in a wide range of activities including energy metabolism, inflammation, circadian rhythm, development, gene regulation through proteins like CREB, and cell survival. GSK3 inhibition can also lead to increases in BDNF levels. GSK3 inhibitors are an active area of research for a variety of diseases. GSK3 is thought to act on amyloid β precursor protein (APP) and modulate activity of both β - and γ -secretases, two enzymes that also affect APP processing. GSK3 is also thought to directly phosphorylate tau. Inhibiting GSK3 therefore leads to reduction of tau phosphorylation and corresponding tau tangle load as well as reduction of A β load. Inhibition of GSK3 may have other neuroprotective roles, such as promoting neurogenesis. A study by [Aron et al., 2025](#) explored transcriptomic and proteomic changes in animal models of AD after being fed a lithium-deficient diet. These analyses revealed significant reductions in synaptic and myelin protein components, and increases in proteins involved in neuroinflammation, among other changes. They found increased expression of GSK3 β mRNA and protein in lithium deficient animals. Treating the lithium-deficient animals with a GSK3 β inhibitor led to reductions in neuroinflammation, A β deposition and tau phosphorylation, and defects in oligodendrocytes. The authors concluded that GSK3 β activation contributes to a range of pathological activities of lithium deficiency.

Often, the effects seen in preclinical research rely on doses that are not easily achieved in the patients but, in this case, low pharmaceutical doses of lithium (for example 0.5 mmol/L) would be expected to inhibit the enzyme ([Sutherland & Duthie, 2015](#)). One pilot clinical trial reported that the phosphorylation of tau proteins (a potential driver of Alzheimer's disease) was reduced by one year of treatment with a low pharmaceutical dose of lithium, roughly 150 to 450 mg of lithium carbonate daily to achieve blood

serum levels of 0.25 to 0.5 mEq/L ([Forlenza et al., 2011](#)) but a higher dose trial in Alzheimer's patients did not yield the same results ([Hampel et al., 2009](#)); Forlenza and colleagues also did not report significant tau reduction in their full dataset ([Forlenza et al., 2019](#)). GSK3 may also phosphorylate α -synuclein ([Snitow et al., 2021](#)).

There are many other potential mechanisms of action of lithium outside of inhibition of GSK3. As reviewed by [Alda, 2015](#), [Hampel et al., 2019](#), and [Hamstra et al., 2023](#), among others, lithium affects ion dynamics and membrane potential, therefore modulating neuronal excitability. It is thought that lithium can more directly affect neurotransmission, such as through affecting membrane transporters and receptors and neurotransmitter synthesis. The effects of lithium on glutamatergic transmission, for instance, is one potential route of neuroprotection. Lithium can modulate a number of molecules involved in cellular signaling cascades, including inositol monophosphate, cAMP and cGMP, and nitric oxide (NO). Some groups have found evidence that lithium can improve mitochondrial function and decrease oxidative stress, potentially in part through affecting NA-K ATPase. Lithium is thought to affect regulation of calcium levels in neurons which can have wide-ranging downstream impacts ([Alda, 2015](#); [Hampel et al., 2019](#)). Lithium treatment is also thought to upregulate Bcl-2, an anti-apoptotic protein ([Can et al., 2014](#)).

Laboratory studies have shown a variety of other potential effects of lithium. Some work has suggested that lithium can increase the activity of stem cells and ramp up the transport of Vitamin B12 and folate into cells, which may in turn protect the brain. Lithium can also increase the number of mitochondria ([Fornai et al., 2008](#)), and increase autophagy, a process by which cells get rid of dysfunctional or unnecessary parts including the aggregated proteins associated with Alzheimer's, Parkinson's, Huntington's disease, and ALS ([Fornai et al., 2008](#); [Sarkar & Rubinsztein, 2006](#)). Lithium treatment has reduced levels of pro-inflammatory cytokines and markers of oxidative stress ([Wilson et al., 2018](#)). In preclinical models, lithium has also been suggested to potentially improve blood brain barrier (BBB) integrity and/or mitigate damage to the BBB, possibly through its anti-inflammatory effects ([Taler et al., 2021](#); [Almeida et al., 2022](#); [Song et al., 2022](#)). Other groups have reported evidence that lithium abrogates ferroptosis in iPSCs derived from an APOE4 homozygous AD patient ([Wang et al., 2026](#)).

A 2025 preclinical study, which garnered media attention, suggested that another formulation of lithium known as lithium orotate may be more effective than lithium carbonate. This study by [Aron et al., 2025](#) first used mass spectrometry to assess relative levels of metals in prefrontal cortex human brain samples and blood samples from patients with MCI or AD as well as cognitively normal controls. Of the 27 metals they tested for, only lithium was significantly reduced in the prefrontal cortex of both MCI and AD patients compared to healthy controls. The levels of lithium in patients with MCI or AD were not

reduced in the cerebellum, an area of the brain relatively spared by AD, or in blood, compared to controls. They also found that levels of cortical lithium were positively correlated with assessments of working memory ($p=0.04$) and the MMSE ($p=0.02$).

The researchers hypothesized that lithium homeostasis was affected by AD and performed further experiments. They subfractionated human prefrontal cortex samples into an A β plaque-enriched insoluble fraction and a soluble fraction and found that lithium levels were significantly lower in the soluble fraction in AD patient samples compared to healthy controls. They also found that lower levels of lithium in the soluble fraction were correlated with lower scores on assessments of cognitive function. Animal experiments also showed that lithium appeared to be sequestered by A β . The researchers then fed wild-type mice as well as two different AD mouse models (3xTG and J20) lithium-deficient chow and found that there was an acceleration of amyloid deposition and phosphor-tau accumulation in the AD mice as well as an increase in levels of A β 42 in the wild-type mice compared to mice fed normal chow. They also observed a significant impairment in learning and memory in AD mice and significant impairment in memory in the wild-type mice when the mice were fed lithium-deficient chow compared to normal chow.

As their initial experiments suggested that lithium was being sequestered by plaques, the researchers hypothesized that lithium was binding to A β plaques via electrostatic interactions. They then compared 16 different lithium salts to assess their ionization capacity, theorizing that a reduced ionization capacity / conductivity might bind less well to the plaques and thus not be sequestered. They found that inorganic salts such as lithium carbonate had the highest conductivity, whereas organic salts had the lowest conductivity. Lithium orotate had the lowest conductivity of their tested salts. *In silico* binding assays in water indicated that lithium does bind to both A β oligomers and fibrils, and that lithium orotate had a lower binding affinity than lithium carbonate. They then compared the effects of lithium carbonate to lithium orotate *in vivo*; all forms of lithium were administered via drinking water at the same elemental lithium concentration. Their experiments showed that there was no difference in serum or hippocampal level of lithium between the two formulations after 7 days of treatment, but that there was less lithium in the insoluble fraction in lithium orotate treated mice compared to lithium carbonate treated mice. Months of lithium orotate treatment both prevented A β and phospho-tau deposition in younger mice and reduced existing plaque and tau burden in older mice; lithium carbonate did not have the same effect at the same dose. Lithium orotate treatment reduced total GSK3 β , activated pTyr216-GSK3 β , and increased levels of nuclear β -catenin. The treatment with lithium orotate also increased expression of the synaptic marker PSD-95, increased oligodendrocyte number, and reduced microgliosis and astrogliosis in these treated mice compared to lithium carbonate treated mice. When the



researchers looked at the effects of lithium orotate treatment on the cognitive function of AD animal models, they found that lithium orotate mitigated the memory and learning deficits, whereas lithium carbonate and sodium orotate did not have these effects.

Lastly, the researchers treated aged wild-type mice with lithium orotate for a year and found that treated animals had reduced astrogliosis, microgliosis, levels of IL-6 and IL-1 β , dendritic spine loss, and learning and memory deficits compared to their vehicle treated wild-type counterparts ([Aron et al., 2025](#)).

This publication by [Aron et al., 2025](#) appears to have revived a previous debate that lithium orotate supplements are often represented as “safer, “natural,” or more effective at reaching the brain than other lithium salts. A German physician, Hans Nieper, heavily promoted the use of lithium orotate, hypothesizing that lithium would remain bound to the orotate until it reached its target tissues (i.e. the brain). In one study from the 1970's, injection with lithium orotate versus lithium carbonate did result in higher levels in the brain of rats ([Kling et al., 1978](#)). However, this study used a high-dose preparation of lithium orotate that probably impaired kidney function and led to slower secretion of lithium from the body ([Smith & Schou, 1979](#)). In other words, lithium orotate did not better penetrate the brain but simply accumulated in brain and body because the kidney failed to remove it quickly. In contrast, when equivalent doses of lithium ion were injected into rats as either lithium orotate, lithium carbonate, or lithium chloride, the resulting levels of lithium across the body and brain were very similar ([Smith, 1976](#)). More recent preclinical studies have not replicated these safety concerns ([Murbach et al., 2021](#)); see ‘Safety’ section for more information.

Other work on lithium orotate is limited. A preclinical paper from 2023 reported that lithium orotate was effective at blocking amphetamine-induced hyperlocomotion, a model of mania, at lower doses than lithium carbonate. Their experiments suggested that lithium orotate has different pharmacokinetic properties than lithium carbonate, with lithium carbonate dissolving more readily than lithium orotate and lithium orotate utilizing different transport mechanisms in the body and across the blood-brain barrier than lithium carbonate. After 14-day dosing, the researchers found that lithium carbonate treatment led to polydipsia, elevated serum creatinine, and increased serum TSH, whereas lithium orotate did not lead to any observed adverse events. In contrast to [Aron et al., 2025](#), this paper reported that lithium orotate treated mice had higher serum and brain levels of lithium than lithium carbonate treated mice at equivalent doses of elemental lithium ([Pacholko & Bekar, 2023](#)). [Aron et al., 2025](#) also did not report changes in water consumption that Pacholko & Bekar observed.

A guest editorial from [Hajek et al., 2026](#) discussed the findings in [Aron et al., 2025](#). While Hajek and colleagues voice appreciation and admiration for the work completed by Aron and colleagues, the editorial brings up several critiques. They point out that for lithium orotate to have different bioavailability than lithium carbonate, lithium orotate would have to be absorbed and circulated as lithium orotate rather than lithium ions. However, Hajek and colleagues assert that in the acid environment of the human stomach, lithium should dissociate to be free in solution, and that no study with oral administration of lithium orotate has shown stable lithium orotate in serum. They also point out that the earliest studies that suggested a difference in pharmacokinetics of lithium carbonate and lithium orotate were from peritoneal administration rather than oral treatment, and that a non-oral route of administration that delivered lithium orotate as such to the blood may in fact show differences in bioavailability that oral administration through food or water may not. Hajek and colleagues suggest that the beneficial actions of lithium orotate treatment on behavior and pathology could in fact be the neuroprotective effects of long-term, low-dose treatment with lithium of any kind. They speculate that the differences seen between lithium carbonate and lithium orotate could be due to the more bitter or metallic taste of lithium carbonate, which theoretically could have reduced the intake of the animals. While Aron and colleagues state that water consumption and lithium levels were the same between groups, Hajek and colleagues wonder whether there was sufficient power to detect a difference in these measures. Hajek et al. suggest that even a subtle difference over the course of the 7-to-9-month treatment experiments could have led to enough of a lower cumulative lithium exposure to lead to different outcomes between the lithium formulations. Moreover, Hajek and colleagues state that the stomach of a mouse is much less acidic than a human, and thus there might be less dissociation of lithium orotate than in humans. This difference in anatomy may also make the preclinical results harder to extrapolate to humans. The guest editorial did not have a potential explanation for why lithium was more present in the insoluble fraction in animals treated with lithium carbonate compared to lithium orotate. Hajek and colleagues call for experiments demonstrating a stable complex of lithium orotate in serum following oral administration in humans to settle this question of whether there is mechanistic plausibility for a difference in pharmacokinetic/pharmacodynamic behavior of lithium orotate compared to lithium carbonate.

A separate commentary in a blog post by [Lowe, 2025](#) did not have the same critiques, and pointed out that magnesium orotate has a different side effect profile than other magnesium salts that may speak to a different ionization properties. [Pacholko & Bekar, 2021](#) also discuss this example of magnesium orotate and the argument that lithium orotate does not dissociate at physiological pH, though they do not discuss whether these arguments account for the physiological pH of the stomach or not. A separate study of magnesium supplements used an *in vitro* model of the human digestive system to compare the

solubility of different commercially available magnesium supplements; their results indicated that magnesium orotate did dissolve to at least some extent in environments mimicking the stomach ([Blancquaert et al., 2019](#)). If or how this translates to lithium orotate is unknown. Pharmacokinetic studies in humans that directly compare different lithium formulations are needed to resolve these questions.

Other groups have explored alternate administration routes of lithium as well as different formulations. A 2025 preclinical study tested intranasal and oral administration of lithium in water or in Ryanodex formulation vehicle (RFV) in wild-type mice and in the 5XFAD mouse model of AD. They found that intranasal administration of lithium in RFV significantly increased brain:blood lithium concentration ratios compared to oral administration and that this intranasal administration protected against memory loss, reduced neuroinflammation, and mitigated loss of some synaptic proteins. They also did not observe any sign of thyroid or kidney toxicity ([Bhuiyan et al., 2025](#)).

Taken together, there is significant preclinical evidence of benefit of lithium in various animal models and via multiple pathways, including but not limited to GSK3. Although these mechanisms sound promising, it is discouraging to note that most of these mechanisms have not been validated in humans. Early studies in animals also suggested that lithium could protect the brain against amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) but the treatment failed to help patients ([Gamez et al., 2013](#), [AlzForum](#)). Whether this can be overcome by formulation, route of administration, or other approach, or whether these effects do not translate to humans, is yet to be determined.

APOE4 interactions:

It is not yet known whether lithium has differential impacts based on APOE status. Some preclinical work in human induced pluripotent stem cells from an APOE4 carrier with AD suggests that treatment with lithium may mitigate some cellular vulnerabilities associated with carrying an APOE4 allele ([Wang et al., 2026](#)). Clinical studies have generally not reported differential effects based on APOE status outside of [Devanand et al., 2022](#), which describes a 12-week trial of lithium in patients with probable AD and primarily explores the efficacy of lithium for agitation. The researchers report that the results of their primary, secondary, and exploratory outcomes were unchanged when APOE4 was used as a covariate. Future studies or re-analysis of existing data can shed more light on the clinical relevance of these early preclinical findings.

Aging and related health concerns: There is some preclinical evidence suggesting potential benefit for health conditions such as stroke, but clinical evidence is lacking.

Types of evidence:

- 3 systematic review and meta-analysis
- 2 cross-sectional studies on telomere length in bipolar patients treated with lithium
- 1 observational study
- 1 review
- Several lifespan studies in worms and flies

It is not yet clear whether lithium use or intake has an effect on lifespan or healthspan. One low-quality study reported that Japanese people living in areas with relatively high content of lithium in tap water had lower overall rates of death than similar people living in areas with relatively low content of lithium in tap water ([Zarse et al., 2011](#)). However, this study has not yet been replicated or tested in other groups of people. It is very possible that the positive results are due not to lithium but to some other shared feature of the Japanese communities living in certain regions that happen to have high lithium content in the water.

While some individual studies have reported that long-term use of pharmaceutical lithium in bipolar patients has been correlated with longer leukocyte telomere length ([Squassina et al., 2016](#); [Martinsson et al., 2013](#)), a 2025 systematic review (n=28 studies) and meta-analysis (n=19 studies) of observational studies reported that while telomere length is significantly shorter in patients with schizophrenia or bipolar disorder compared to healthy controls, that neither lithium nor antipsychotic treatment modified this difference. The researchers note that there was high heterogeneity in their findings ([Sánchez-González et al., 2025](#)). It should also be noted that long-term lithium use can also carry serious risks including kidney damage (see the 'Safety' section for further discussion).

Lifespan or healthspan extension has not been reported in mammals at any dose. In worms and flies, high doses of lithium have shortened lifespan ([Castillo-Quan et al., 2016](#)) although low doses of lithium have increased lifespan in several ([Castillo-Quan et al., 2016](#); [Zarse et al., 2011](#); [Tam et al., 2014](#)) but not all studies ([Zhu et al., 2015](#)). The suggested mechanism of action was inhibition of GSK3 β leading to NRF2 activation ([Castillo-Quan et al., 2016](#)). In contrast, autophagy has been suggested as a primary mechanism of action in other invertebrate lifespan studies on lithium (e.g. [Tam et al., 2014](#)).

There are some hints of potential benefits of lithium in the context of vascular injury, atherosclerotic plaque formation, cardiovascular disease, or stroke, though clinical data only exists for the latter, and that clinical data is sparse. The hypothesis is that these effects are mediated by lithium's anti-inflammatory, anti-apoptotic, and/or antioxidant actions; careful human studies are needed to test this hypothesis ([Almeida et al., 2022](#); [Chen et al., 2022](#); [Ponzer et al., 2023](#)).

Safety: Lithium requires titration to the therapeutic range. Severe lithium toxicity can risk coma or even death. Therapeutic doses can lead to GI side effects, weight gain, tremor, and affect renal and thyroid function. Monitoring and low doses can mitigate risks.

Types of evidence:

- 4 meta-analyses or systematic reviews
- 3 clinical trials
- 3 observational studies
- 1 commentary on an observational study
- 1 survey of individuals who use lithium supplements
- 3 professional resources pages
- 6 reviews
- 1 laboratory study

Too-high doses of lithium can cause lithium toxicity. Signs of lithium toxicity are “obvious and can be identified and managed easily”, but ignoring these signs can be fatal. Symptoms of mild lithium toxicity often include nausea, vomiting, lethargy, tremor, and fatigue. Moderate toxicity symptoms include confusion, agitation, delirium, tachycardia, and hypertonia. Severe lithium toxicity can manifest as coma, seizures, hyperthermia, and hypotension, and can lead to brain damage or death. Below is a table of the serum lithium levels typically associated with each grade of toxicity, expressed in units of mEq/L lithium ([Hedya et al., 2023](#)); note that the therapeutic range is thought to be broadly between 0.4 and 1.2 mEq/L ([Nolen et al., 2019](#)).

Grade of Toxicity	Associated Serum Lithium Level
Mild	1.5 to 2.5 mEq/L
Moderate	2.5 to 3.5 mEq/L
Severe	More than 3.5 mEq/L

Common side effects in patients with psychiatric disorders include gastrointestinal side effects like nausea and diarrhea, excessive thirst and urination, weight gain, exacerbation of psoriasis, and hand tremor. Vomiting is reported to be an infrequent side effect and is typically associated with toxicity; tremor, on the other hand, is reported to be common as an adverse event, with toxicity-related tremors typically being more irregular, widespread, and severe, and are usually accompanied by other signs of toxicity. Lithium, especially long-term use of lithium, can affect kidney function as well as thyroid and parathyroid gland function, and individuals should discuss monitoring with their physician ([Drugs.com](#); [Chokhawala et al., 2024](#)). Typical monitoring guidelines include baseline kidney and thyroid function assessments, with repeat assessments once or twice annually. Noting patient weight and performing assessments for prediabetes, diabetes, or dyslipidemia can also be of use. In patients older than 50, a baseline ECG is also recommended ([Chokhawala et al., 2024](#)). For older adults, the International Society for Bipolar Disorders (ISBD) further recommends frequent assessments of renal function every 3 to 6 months, metabolic and endocrine testing every 6 months, and yearly hematology, along with routine assessments of gait, tremor, and cognitive function ([Shulman et al., 2019](#)).

Cognitive impairment has also been reported by patients, though it is very difficult to disentangle the effects of lithium vs. the effect of other drugs in use and the underlying disorder itself ([Gitlin et al., 2016](#)). Other side effects can include cardiac symptoms such as bradycardia, leukocytosis and aplastic anemia, acne, rash, and weight gain ([Chokhawala et al., 2024](#)).

Age-related decreases in renal clearance of lithium could lead to higher lithium levels and concomitant side effects and/or toxicity. Several medications that are commonly used by older adults can also interact with lithium and lead to higher levels of lithium in the blood. Some symptoms of toxicity such as tremor or neurological disturbance can also be misdiagnosed as an age-related condition rather than as lithium toxicity ([Shulman et al., 2019](#)). According to task force reports from the ISBD, target serum concentration of lithium should be lower in older adults ([Nolen et al., 2019](#)). The consensus recommendation of the ISBD Older Adults with Bipolar Disorder Task force was that the standard blood lithium level in those 60 to 79 years should be 0.4 to 0.8 mmol/L. In adults 80 years or older, the standard serum level should be 0.4 to 0.7 mmol/L. The task force also reached consensus that common signs of lithium toxicity among older adults with bipolar disorder included impaired ability to sustain and shift attention, delirium, tremor, ataxia, and gastrointestinal symptoms such as nausea and vomiting ([Shulman et al., 2019](#)).

The side effect profile in older adults without a psychiatric diagnosis, whether cognitively intact or with some degree of cognitive impairment, is also an important question. A systematic review and meta-

analysis of 6 publications of RCTs with 394 participants with MCI or AD reported that the pooled risk of adverse events was numerically greater in the lithium group compared to the placebo group, but that this was not statistically significant (RR=2.28; 95% CI 0.11 to 47.36). There was also no significant difference in serious adverse events between groups (RR=1.25; 95% CI 0.63 to 2.49) ([Pereira da Silva et al., 2026](#)). Details on specific trials are included below.

One clinical trial treated elderly patients with a low drug dose of lithium and published results in several papers. In their first paper covering 45 participants for 1 year, the authors report similar rates of adverse events in lithium and placebo groups, with no standout concerns ([Forlenza et al., 2011](#)). A follow up paper reported more in-depth safety outcomes for 61 total participants after four years of lithium treatment. Although the low dose was well-tolerated by the elderly patients with few reported side effects, some red flags were raised including increased incidence of diabetes, arrhythmia, significant weight gain, and possibly hypothyroidism, although no difference was seen in kidney function, gastritis, or dyslipidemia. There were significantly more adverse events in the lithium group as compared to placebo, especially when looking at adverse events that interfered with daily functioning ([Aprahamian et al., 2014](#)). Decreased metabolism in key brain areas was also reported ([Forlenza et al., 2014](#)). In total, 52 of the 61 participants completed the double-blind stage of the trial, one of whom experienced clinical symptoms of lithium toxicity. Mean serum levels of lithium in the study were approximately 0.4 mEq/L. Of the double-blind phase completers, 40 finished the extension study. There was no statistically significant difference in reason for discontinuation or withdrawal between groups ([Forlenza et al., 2019](#)).

A 2022 study assessed the use of lithium for symptoms of agitation and/or aggression in patients with AD. The randomized controlled double-blinded study enrolled 77 patients and randomized to either placebo or lithium doses of 150 to 600 mg daily to achieve a serum lithium level of 0.2 to 0.6 mmol/L. Dosing lasted for 12 weeks. The authors report that there were no significant differences in rates of serious adverse events between groups, nor any significant difference in incidence of specific adverse events between the two groups. There was a trend towards increased gait instability in patients receiving lithium ($p=0.055$) and potentially a trend towards changes in thyroid hormone levels in the lithium group, though the latter was potentially confounded by prior history of thyroid disease ([Devanand et al., 2022](#)).

A small pilot study of 11 patients with MCI assessed biomarkers and safety of lithium treatment for 9 weeks; doses started at 100 mg daily and steadily increased to 400 mg daily. Of the 11 patients, 4 withdrew due to reported side effects, though there was no association between lithium blood concentration and withdrawal. No serious adverse events were reported. Six of the 11 patients reported side effects, and those of moderate or severe intensity included: metallic taste, dry mouth, nausea,

decreased concentration, insomnia, or confusion. Feeling drowsy or lethargic was the most commonly reported adverse event overall ([Duthie et al., 2019](#)).

A study in MCI randomized patients to receive either lithium or matching placebo for 2 years. Patients received doses of up to 300 mg of lithium once daily; the average serum concentration of lithium was 0.17 mEq/L, with a maximum of 0.5 mEq/L. There was one death in the study in a patient in the placebo group. There were 41 serious adverse events, with 25 in the lithium group and 16 in the placebo group; none were definitely related to the study drug. Common adverse events included diarrhea, fatigue, tremor, and increased creatinine and TSH levels. There was no significant difference in study discontinuation between the lithium (34%) and placebo group (38%) ([Gildengers et al., 2026](#)).

A small 12-week RCT study compared the effects of lithium to placebo in 16 patients with FTD. Patients were titrated up to a maximum of 600 mg per day of lithium to reach a serum level of 0.2 to 0.6 mmol/L or matching placebo. The most common adverse event in the lithium group was diarrhea, which was reported by 57% of the participants. Three less common adverse events were possibly related to lithium: one episode of syncope and two instances of falls, both of which were categorized as serious adverse events and one which involved a broken rib ([Zide et al., 2025](#)).

The adverse event profile of low-dose lithium is also an area of research interest. A systematic review assessed the health effects of low dose lithium (as defined by serum levels of approximately ≤ 0.6 mmol/L) in 18 studies in a wide array of populations, including AD, bipolar disorder, former drug or alcohol users, and multiple sclerosis. The review reported that low-dose lithium was not associated with a greater risk of adverse events or serious adverse events compared to placebo ([Strawbridge et al., 2023](#)).

Lithium can also be obtained through diet, water, and in dietary supplements. The safety profile of these sources of lithium are not well studied or well understood, though their availability and decades of use without significant published safety concerns should be noted ([Strawbridge et al., 2025](#)). Higher doses have serious health risks whether obtained from supplements or pharmaceutical drugs ([Balon, 2013](#)). At least one case has been documented of lithium toxicity in a patient who ingested 18 pills of lithium orotate, equivalent to 82.7 mg of elemental lithium. The patient reported nausea and vomiting, and she had a mild tremor. Her serum lithium levels reached 0.4 mEq/L in the emergency room. The nausea and tremor resolved after 3 hours of observation, and the patient was transferred to a psychiatric care for further care. For comparison, 82.7 mg is lower than the amount of lithium obtained in standard pharmaceutical doses of lithium carbonate; for instance, a 900 mg dose of lithium carbonate contains approximately 169.2 mg of elemental lithium ([Pauze & Brooks, 2007](#)).

The exact formulation of lithium may merit additional safety attention. For instance, preclinical studies have implicated orotate in inducing hepatic lipogenesis, tumorigenesis, insulin resistance, and renal effects (reviewed in [Murbach et al., 2021](#)). Other studies did not replicate some of these effects, and a 28-day toxicology study of lithium orotate in rats did not report any safety flags ([Murbach et al., 2021](#)). Whether any of these preclinical findings translate to clinical relevance is not known. Very few studies of lithium orotate have been performed in humans, though several studies cite reassurance from the use of lithium orotate in supplement form for decades with no reported deaths or serious side effects ([Devadason, 2018](#)).

Drug interactions:

Lithium may interact with at least 738 drugs; of these interactions, 195 are major interactions, 506 are moderate, and 37 are minor. Notable interactions include but are not limited to buspirone, fentanyl, St. John's wort, tramadol, tryptophan, antidepressants and antipsychotics, and MAO inhibitors ([Drugs.com](#)). Common drugs like over-the-counter anti-inflammatory drugs (for example, ibuprofen, celecoxib/Celebrex, or indomethacin), caffeine, theophylline, antidepressants, anti-hypertensive medications, and others can interact with lithium and change the dose of lithium that might be safe or effective ([Grandjean & Aubry; 2009](#); [D'Souza et al., 2011](#); [McKnight et al., 2012](#)).

Older people are much more vulnerable, with higher serum levels in response to the same dose and with risks from interactions with comorbidities and other drugs. The risks of lithium treatment are particularly high in people with renal or cardiovascular disease, hypothyroidism, previous neuroleptic malignant syndrome, seizures, dehydration (including diarrhea and excessive sweating), sodium depletion, or if they take diuretics or haloperidol. The American Geriatrics Society (AGS) Beers Criteria for Potentially Inappropriate Medication Use in Older Adults strongly recommends against the concurrent use of lithium with ACE inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors, or loop diuretics as simultaneous use increases the risk of lithium toxicity. They recommend monitoring blood lithium concentrations if the medications must be used together ([AGS Beers Criteria Update Expert Panel, 2023](#)).

More information on lithium side effects and interactions with medications, alcohol, and food can be found at [Drugs.com](#) and [www.mayoclinic.org](#).

Research underway:

There are currently 75 ongoing studies registered on clinicaltrials.gov that involve lithium in some way. Many of these studies merely mention lithium as a component of a medical device such as a battery, and others are exploring new formulations of lithium such as AL001, a crystallized version of lithium (e.g. [NCT06921590](https://clinicaltrials.gov/ct2/show/study/NCT06921590)). Of the studies testing lithium as an intervention, many focus on treatment of psychiatric conditions like bipolar disorders. Six studies involve lithium as a treatment for cognition in some way.

[NCT07459959](https://clinicaltrials.gov/ct2/show/study/NCT07459959) is a RCT that is estimated to begin in fall of 2026. The study intends to enroll 40 patients with mild, biomarker-confirmed AD. Participants will be randomized to receive lithium orotate capsules or matching placebo for a total of 9 weeks. There will be a structured titration of the lithium orotate and placebo, with patients receiving 240 mg per day, 480 mg per day, and 720 mg per day for the first, second, and third week, respectively. Patients will then continue on the highest tolerable dose until week 9. The study team notes that 240 mg of lithium orotate contains approximately 10 mg of elemental lithium; there is less elemental lithium per mg in lithium orotate vs. lithium carbonate. There are several different primary outcome measures for safety, tolerability, and feasibility. Secondary outcome measures include changes in CSF lithium levels, neurofilament light, neuropsychiatric symptoms, and cognition as measured by delayed recall. This study is estimated to complete in summer of 2029.

[NCT06339034](https://clinicaltrials.gov/ct2/show/study/NCT06339034) is an RCT testing the use of lithium in patients with Parkinson's disease (PD). The study planned to enroll 20 patients with PD and randomize them to receive either lithium (10 mg doses twice a day containing 5 mg elemental lithium per capsule) or matching placebo. Dosing lasted for 24 weeks. The primary outcomes are change in MRI-derived free water levels, change in a potential PD blood biomarker known as Nurr1, and change in serum neurofilament light levels. There are a variety of secondary outcome measures including assessments of PD disease progression, cognition, neuropsychiatric symptoms, disease biomarkers, and potential target engagement biomarkers such as the ratio of pS9 to total GSK3 β levels in blood cells. This study is estimated to complete in fall 2026. [NCT06592014](https://clinicaltrials.gov/ct2/show/study/NCT06592014) is a follow-on open-label extension study for participants who complete the above trial. Participants who enroll in this study will receive lithium aspartate to reach a serum lithium level of 0.25 to 0.5 mmol/L for 24 weeks. The primary outcome measures are neuroimaging and blood biomarkers; secondary outcome measures include a number of other blood biomarkers and assessments of PD symptoms.

[NCT06051240](#) plans to examine whether treatment with lithium can mitigate or prevent cognitive decline after brain radiotherapy in 84 pediatric patients. The study will randomize pediatric patients at least 5 years of age to either 42 mg (6 mmol) lithium or matching placebo. Participants will be dose escalated to a target serum level of 0.5-1.0 mmol/L lithium. They will receive treatment for 6 months and then be followed for up to 7 years to assess long-term outcomes. The outcome measures include measures of cognition, feasibility, adverse events, and assessments of white matter integrity through MRI.

[NCT05593627](#) is an ongoing study that is assessing the effects of lithium carbonate on post-operative sleep and cognition in patients undergoing a specific type of surgery. The trial aimed to enroll 62 patients to randomize to receive either lithium carbonate (250 mg) or placebo (calcium carbonate, 500 mg) after their heart valve surgery with cardiopulmonary bypass. The primary outcome measure is sleep quality as measured by polysomnography on the second postoperative night. Other outcome measures include cognitive function as assessed by MMSE on post-operative day 7.

[NCT06662526](#) is an RCT in patients aged 55 to 75 who have been diagnosed with mood disorders. The study plans to enroll 250 such patients and randomize them to receive 50 mg of lithium per day for 5 years or matching placebo. The primary outcome of the study is the incidence of MCI in the two groups. Secondary outcomes include assessments of neuropsychiatric health and cognitive function. The study was predicted to start in late 2024 and complete in late 2030; however, no updates have been posted to confirm whether the trial has started enrolling.

[NCT06776848](#) is a randomized open labeled trial in patients with TBR1 mutations; these mutations cause neurocognitive disorders. The trial aims to enroll 12 patients with confirmed TBR1 mutations. The participants will then be observed for 6 to 12 months before starting lithium carbonate treatment. Lithium will be dosed to an unspecified blood concentration of lithium. The outcome of the study is the change in a measure of personal and social skills known as the Vineland II Adaptive Behavior Scale during lithium treatment compared to the untreated observation phase.

Search terms:

Pubmed, Google: lithium, lithium orotate, lithium carbonate

- Dementia, Alzheimer's, stroke, safety, cognition, diabetes

Websites visited for lithium:

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- [Examine.com](https://examine.com)
- Geroprotectors: [C. elegans](#); [human](#)
- [Drugs.com](https://drugs.com)
- [WebMD.com](https://webmd.com)
- [PubChem](https://pubchem.ncbi.nlm.nih.gov)
- [DrugBank.ca](https://drugbank.ca)
- [Cafepharma](https://cafepharma.com)

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