Lithium and GSK3-beta March 20, 2024

A question: what are your thoughts on lithium as a mineral supplement (should the RDA be about 1 mg a day, like zinc, copper, etc.)?

I am in the process of researching this issue. The areas of the world that have the highest levels of lithium in drinking water have lower rates of depression, suicide, less incarceration of youth for drug use and violent behavior, and lower rates of dementia. Lithium increases longevity in fruit flies and C elegans. One Japanese water survey study found the possibility of an increased longevity effect of higher lithium levels in drinking water.

Lithium in water is negatively linked with changes in AD mortality, as well as obesity and type 2 diabetes, which are important risk factors for AD. https://www.mdpi.com/2073-4409/10/2/255. Lithium improves blood sugar levels in patients with diabetes and may prevent diabetes and obesity?

GSK3-beta is critical in dementia. It is the enzyme that hyper-phosphorylates Tau protein that leads to neurofibrillary tangles in Alzheimer's disease, as with Amyloid Beta pleated sheets. Lithium is a direct inhibitor of GSK3-beta. More on this in the word document below.

The dose for bipolar disorder is 900 to 1800 mg per day, with blood levels of 0.8-1.2 mmol/L. The dosing in the mild cognitive impairment studies had blood levels in the range of 0.25 - 0.5 mmol/L (60-70% lower than in bipolar disorder). This showed slowing of cognitive decline over 4 years, and with follow up 8 years later the group that had taken lithium scored 25/30 on the Mini Mental Status Exam (MMSE), while those on placebo scored 18/25, even though neither group had continued lithium for those 8 years.

But even lower doses may be helpful, including microdosing at 1-5 mg per day. We don't know yet. There is one Brazilian study with 300 mcg per day that showed positive results for mild cognitive impairment, but this has not yet been confirmed by others.

A very old study used 400 mcg of lithium and saw increased scores for happiness, friendliness, energy, etc. I have attached the PDF. I am giving microdosing a trial on myself. I am finding I am listening to much more classical music (like when I was much younger) and worrying less about getting everything done (pros and cons on this?).

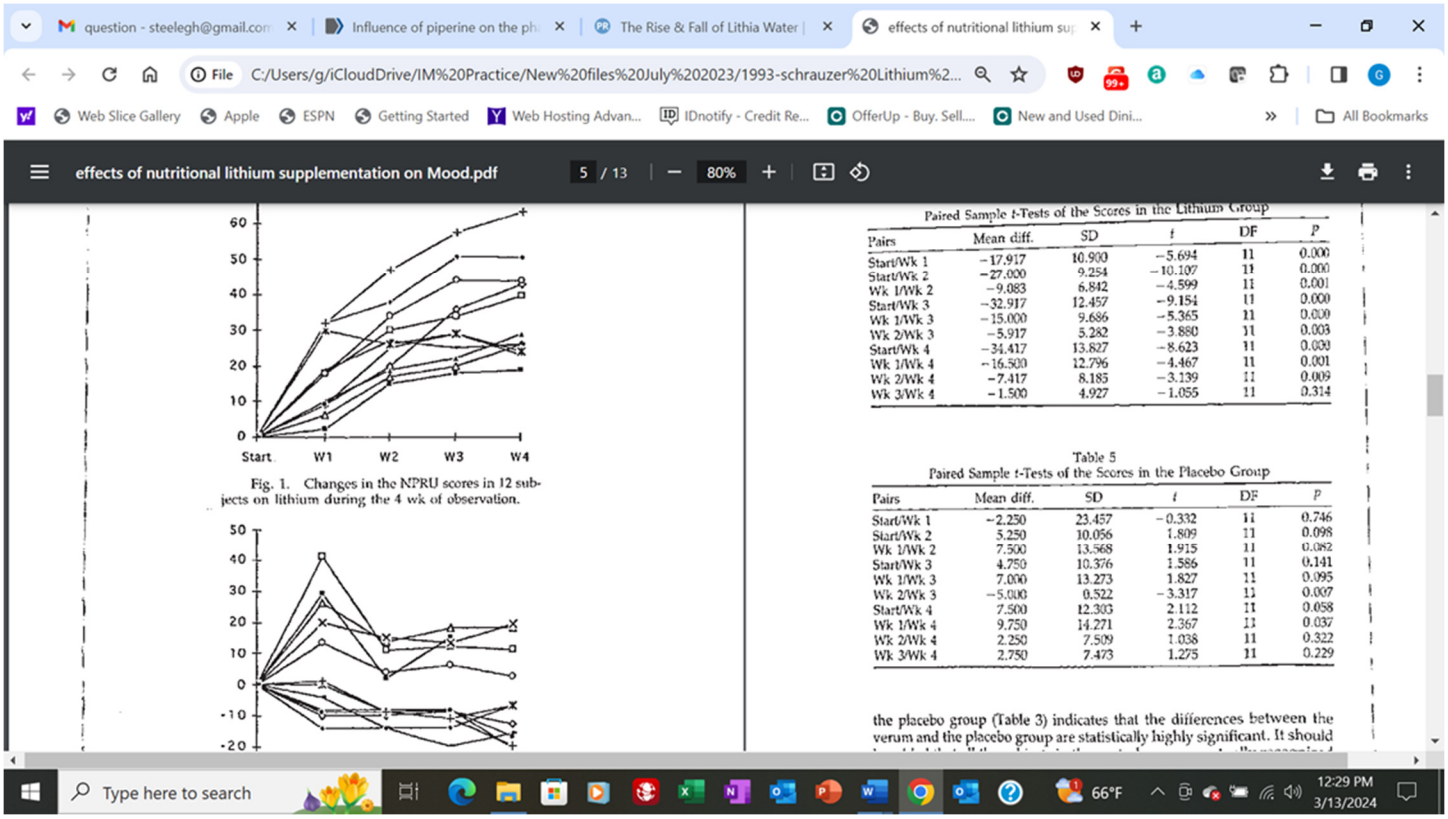
Effects of nutritional lithium supplementation on mood: a placebo-controlled study with former drug users

GN Schrauzer, E de Vroey. Biological trace element research, 1994•Springer

https://scholar.google.com/scholar_lookup?journal=Biol+Trace+Elem+Res.&title=Effects+of+nutritional+lithium+supplementation+on+mood.+A+placebo-controlled+study+with+former+drug+users&author=GN+Schrauzer&author=E+de+Vroey&volume=40&publication_year=1994&pages=89-101&pmid=7511924&doi=10.1007/BF02916824&

A total of 24 subjects, 16 males and 8 females, average age 29.4±6.5 y, were randomly divided into two groups. Group A received 400 µg/d of lithium orally, in tablets composed of a naturally lithium-rich brewer's yeast, for 4 wk. Group B was given normal, lithium-free brewer's yeast as a placebo. All the subjects of the study were former drug users (mostly heroin and crystal methamphetamine). Some of the subjects were violent offenders or had a history of domestic violence. The subjects completed weekly self-administered mood test questionnaires, which contained 29 items covering parameters measuring mental and physical activity, ability to think and work, mood, and emotionality. In the lithium group, the total mood test scores increased steadily and significantly during the period of supplementation. The 29 items were furthermore placed into three subcategories reflecting happiness, friendliness, and energy, as well as their negative counterparts. In Group A, the scores increased consistently for all subcategories until wk 4 and remained essentially the same in wk 5. In Group B, the combined mood test scores showed no consistent changes during the same period. The only positive change in some members of Group B occurred during wk 1 and was attributed to a placebo effect. In Group B, the placebo effect was noticeable for the subcategories of energy and friendliness; the happiness scores declined during the entire period of observation.

Based on these results and the analysis of voluntary written comments of study participants, it is concluded that lithium at the dosages chosen had a mood-improving and stabilizing effect.



Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial

02 January 2018 Orestes V. Forlenza

Forlenza OV, Diniz BS, Radanovic M, Santos FS, Talib LL, Gattaz WF. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. British Journal of Psychiatry. 2011;198(5):351-356. doi:10.1192/bjp.bp.110.080044

https://www.cambridge.org/core/journals/the-british-journal-of-psychiatry/article/diseasemodifying-properties-of-longterm-lithium-treatment-for-amnestic-mild-cognitive-impairment-randomised-controlled-trial/C673342DBC81E80462318BF208B9A8F7

Method: Forty-five participants with aMCI were randomised to receive lithium (0.25–0.5 mmol/l) (n = 24) or placebo (n = 21) in a 12-month, double-blind trial. Primary outcome measures were the modification of cognitive and functional test scores, and concentrations of cerebrospinal fluid (CSF) biomarkers (amyloid-beta peptide (Aβ42), total tau (T-tau), phosphorylated-tau) (P-tau). Trial registration: NCT01055392.

Results: Lithium treatment was associated with a significant decrease in CSF concentrations of P-tau (P = 0.03) and better perform-ance on the cognitive subscale of the Alzheimer's Disease Assessment Scale and in attention tasks. Overall tolerability of lithium was good and the adherence rate was 91%.

Conclusions: The present data support the notion that lithium has disease-modifying properties with potential clinical implications in the prevention of Alzheimer's disease.

https://www.mdpi.com/2073-4409/10/2/255

Lithium and Therapeutic Targeting of GSK-3 2021

Alzheimer's disease (AD) is the most common form of neurodegenerative disease with increasing prevalence in an aging population [89]. Two pathologic findings characterize AD, neurofibrillary tangles (NFTs) and amyloid plaques, and both are promoted by GSK-3. NFTs are intracellular deposits of tau protein, a microtubule stabilizer that is regulated by phosphorylation; pathologic hyperphosphorylation of tau disrupts microtubules and promotes development of NFTs [90]. GSK-3 phosphorylates tau in vitro and in vivo at several residues, which can accelerate aberrant tau aggregation and resultant neurodegenerative phenotypes.

Second, β-amyloid (Aβ) peptides (primarily Aβ40 and Aβ42) accumulate in extracellular amyloid plaques. Plaque formation precedes tau pathology in AD and occurs through cleavage of the amyloid precursor protein (APP) into Aβ by β- and γ-secretases [99]. APP processing is also regulated by GSK-3. Both APP and presenilin-1 (PS1), which is part of the γ-secretase complex, are mutated in familial forms of AD, leading to increased accumulation of the more pathogenic Aβ42 peptide. Both APP and PS1 are GSK-3 substrates [100,101,102,103,104,105] and inhibition or knockdown of GSK-3 impairs APP processing, reducing generation of Aβ40/42 in mouse brain and cell culture models.

As GSK-3 plays roles in both NFT formation and APP processing, GSK-3 has been a focus of extensive study for pharmacological interventions in AD. Inhibition with lithium and other agents in preclinical studies reduces Aβ mediated neurotoxicity, improves behavioral phenotypes, and rescues neuronal loss [**105**,**116**,**117**,**118**,**119**]. In addition, retrospective studies, meta-analyses, and a randomized controlled trial with patients with mild cognitive impairment showed that lithium prevented cognitive decline in patients with mild cognitive impairment when compared to matched patients not taking lithium [**120**,**121**,**122**].

Lithium in water is negatively linked with changes in AD mortality, as well as obesity and type 2 diabetes, which are important risk factors for AD. https://www.mdpi.com/2073-4409/10/2/255

A recent, nationwide, population-based study conducted in Denmark indicated a negative association between trace lithium in ground water and the incidence of dementia across different geographical regions. Similarly, lithium concentrations in drinking water in several counties in Texas, USA were negatively associated with mortality rates because of Alzheimer's disease.

https://pubs.acs.org/doi/abs/10.1021/cn5000309

Neuroprotective Effects of Lithium: Implications for the Treatment of Alzheimer's Disease and Related Neurodegenerative Disorders 2014

Lithium is a well-established therapeutic option for the acute and long-term management of bipolar disorder and major depression. More recently, based on findings from translational research, lithium has also been regarded as a neuroprotective agent and a candidate drug for disease-modification in certain neurodegenerative disorders, namely, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and, more recently, Parkinson's disease (PD). The putative neuroprotective effects of lithium rely on the fact that it modulates several homeostatic mechanisms involved in neurotrophic response, autophagy, oxidative stress, inflammation, and mitochondrial function. Such a wide range of intracellular responses may be secondary to two key effects, that is, the inhibition of glycogen synthase kinase-3 beta (GSK-3β) and inositol monophosphatase (IMP) by lithium. In the present review, we revisit the neurobiological properties of lithium in light of the available evidence of its neurotrophic and neuroprotective properties and discuss the rationale for its use in the treatment and prevention of neurodegenerative diseases.

Lithium may reduce risk of dementia : Clinical use of lithium is associated with a lower incidence of dementia in old age (Kessing *et al*, 2010; Nunes *et al*, 2013). Moreover, excellent lithium responders have preserved cognition (Rybakowski and Suwalska, 2010). Lithium-treated patients have better visual memory than nonlithium patients (Bersani *et al*, 2016; Quartini *et al*, 2016). In addition, minute doses of lithium (150 mg/day) exceed placebo in slowing the rate of cognitive deterioration over 1 year in elderly women with mild cognitive impairment (Forlenza *et al*, 2011). Positive effects of micro doses of lithium have been reported in Alzheimer's dementia (Nunes *et al*, 2013).

Lithium has neurotropic and neuroprotective effects : Lithium is associated with increases in hippocampal and cortical volume. This is likely based on its ability to increase neuroprotective factors BDNF and BCl-2 and decrease apoptotic (cell death factors) BAX and P53 (Malhi *et al*, 2013; Rowe and Chuang, 2004). It increases neurogenesis and gliogenesis. In animal models, lithium lessens the size of lesions associated with AID neurotoxicity, ischemic/hemorrhagic stroke, traumatic brain/spinal cord injury (TBI/SCI), Huntington's disease (HD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), fragile X syndrome (FXS), Parkinson's disease (PD), retinal degeneration, multiple sclerosis (MS), alcohol-induced degeneration, Down syndrome, spinocerebellar ataxia-1, and irradiation (Chiu *et al*, 2013).

Lithium increases telomere length: Lithium increases the length of telomeres whose preservation is necessary for maintaining both physical and psychiatric health. Lithium's effects on telomeres occurs as a direct result of increasing the activity of the telomere elongation enzyme—telomerase (Martinsson *et al*, 2013). The longer one is on lithium, the more normal the telomere length becomes (Squassina *et al*, 2016). Telomeres are shortened by childhood stressors, greater numbers of depressive episodes, and implacable anger, whereas they are lengthened by exercise, a good diet, mindfulness/meditation, and having positive and altruistic goals in life (Blackburn *et al*, 2015; Epel *et al*, 2004).

Lithium decreases incidence of some medical illnesses : Lithium may decrease the incidence of some neurological disorders such as seizures, amyotrophic lateral sclerosis (ALS), and dementia NOS, as well as myocardial infarction (Prosser and Fieve, 2016). Lithium, in a dose-related manner, also lowers the incidence of some cancers (Huang *et al*, 2016). It also increases longevity in humans and several animal species (Zarse *et al*, 2011). It also reduces all-cause mortality in patients with bipolar disorder (Toffol *et al*, 2015). Whether any of these effects are secondary to its effects in lengthening telomeres remains to be demonstrated.

Microdose Lithium Treatment Stabilized Cognitive Impairment in Patients with Alzheimer's Disease

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A lower incidence of dementia in bipolar patients treated with lithium has been described. This metal inhibits the phosphorylation of glycogen-synthase-kinase 3-α and β, which are related to amyloid precursor protein processing and tau hyperphosphorylation in pathological conditions, respectively. Following the same rationale, a group just found that lithium has disease-modifying properties in amnestic mild cognitive impairment with potential clinical implications for the prevention of Alzheimer's Disease (AD) when a dose ranging from 150 to 600 mg is used. As lithium is highly toxic in regular doses, our group evaluated the effect of a microdose of 300μg, administered once daily on AD patients for 15 months. In the evaluation phase, the treated group showed no decreased performance in the mini-mental state examination test, in opposition to the lower scores observed for the control group during the treatment, with significant differences starting three months after the beginning of the treatment, and increasing progressively. This data suggests the efficacy of a microdose lithium treatment in preventing cognitive loss, reinforcing its therapeutic potential to treat AD using very low doses.