



NATURAL MEDICINE JOURNAL **RESEARCH GUIDE**

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CLINICAL APPLICATIONS OF **LOW-DOSE LITHIUM** MENTAL HEALTH, COGNITION, AND MORE

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Lithium as a Dietary Supplement

When we think of lithium we may think of batteries or the potent bipolar prescription. We may not think of an all-natural dietary supplement. But thanks to decades-long research, including recent compelling data specifically regarding the brain, a form of low-dose nutritional lithium has made its way into integrative medicine. The growing clinical interest in lithium has been sparked by robust epidemiological analysis and a long history of use as a healing tonic.

The History of Lithium

The naturally occurring trace mineral lithium has been a part of human health since the dawn of time. It is said that just minutes after the Big Bang, protons and neutrons combined to form hydrogen, helium, and lithium. While it has been around for billions of years, lithium wasn't officially identified until 1817. There is much we are still learning about this lightweight, soft mineral naturally found in rock, soil, water, and some foods.



Perhaps the most fascinating aspect of lithium's health effects can be found in drinking water research. Over the past few years, mounting scientific evidence demonstrates that people who live in areas with lithium-rich soil and water have significantly lower rates of aggression, homicide, and suicide compared to people living in areas with low levels of lithium in soil and water.

In addition to the health benefits from drinking water with lithium, for centuries individuals have touted the healing effects of soaking in mineral waters that contain lithium. Despite nutritional lithium's clear benefits for populations around the world, pharmaceutical prescription lithium is what has garnered the most scientific attention.

The medicinal use of lithium dates back to the mid-1800s when it was first used in high amounts to treat gout and then used on the bladder, kidneys, and gallstones. The earliest use of lithium in psychiatry took place in 1870, but it didn't become popular until 1954 after the publication of a randomized controlled trial involving lithium treatment of mania. In the 1970s, the Federal Food and Drug Administration approved lithium for use in psychiatry making the United States the 50th country to approve the prescription.

Throughout the 19th and 20th century lower dose lithium was used to fortify some foods and beverages. In fact, the popular lemon-lime soda known as 7-Up contained lithium citrate until 1950 and was originally marketed to cure hangovers and lift the mood. While lithium is no longer in beverages, today lithium is found naturally in water and some foods such as grains and vegetables. The Environmental Protection Agency estimates that the daily dietary intake of lithium in the United States today is from 0.6 to 3.1 mg, and it is reported that people living in Northern Argentina consume as much as 30 mg per day.

Low-dose lithium is also available as a dietary supplement. There are many distinguishing factors between pharmaceutical lithium carbonate and nutritional lithium with the first being dose. In high doses that can range from 900 mg to 1,200 mg, lithium is a drug that may have serious side effects. In low-dose ranges from 1 mg to 20 mg, lithium is a trace mineral important to many biochemical processes in the human body.

Nutritional Low-Dose Lithium

For many patients with bipolar disorder, prescription lithium can be life-saving and extremely effective at improving disease progression and quality of life. It has been used for nearly 70 years to both reduce and treat bipolar episodes and symptoms of depression. It is indicated as a first-line bipolar treatment especially with patients who are at risk of suicide. Unfortunately, compliance can be a significant issue due to the serious side effects of lithium carbonate, especially with long-term use. Side effects can include:

- Hand and postural tremors
- Nausea, vomiting, and diarrhea
- Fatigue and lethargy
- Inability to concentrate and lack of mental clarity
- Weight gain

In addition to the above side effects, lithium carbonate can damage the kidneys and thyroid. There is nearly a 6-fold increased risk of hypothyroidism with lithium carbonate use compared to placebo and detrimental effects on the kidneys with long-term use are common. Nutritional lithium does not have this effect or the many side effects associated with lithium carbonate.

The absorption of nutritional lithium is thought to be more efficient than with pharmaceutical lithium carbonate. That's why higher doses of lithium carbonate are used to force the lithium ions into the cells. Prescription doses of lithium carbonate are 50 to 300 times higher than what typically occurs naturally with food and water. These high doses contribute to the many side effects, especially the damage to kidneys and thyroid.

Low-dose nutritional lithium, on the other hand, is more bioavailable because it can transport the lithium ions intact through the cell membrane much more effectively than lithium carbonate. Nutritional lithium is nearly equal in size and permeability to sodium and can efficiently make its way through sodium channels to the interior of the cells.

A likely reason why low-dose nutritional lithium has such significant health benefits is that it works along many different pathways.

Multiple Mechanisms

To determine exactly how lithium exerts its therapeutic effects, researchers analyzed the brain of patients with bipolar disorder. Bipolar disorder involves abnormalities in several parts of the brain including the hippocampus, amygdala, and striatum. As it turns out, lithium positively influences several of these same brain regions via numerous mechanisms, which is perhaps one of the most intriguing and important aspects of the health-promoting benefits of this trace mineral. Let's take a closer look at some of these key mechanisms.

Neuroprotective. The neuroprotective effects of lithium occur in several regions of the brain including the amygdala, hippocampus, and prefrontal cortex. Neuroimaging shows that lithium can help preserve grey matter. Lithium also modulates several homeostatic mechanisms related to autophagy, inflammation, mitochondrial function, neurotrophic response, and

oxidative stress. Lithium inhibits glycogen synthase kinase activity, thereby influencing cell division, metabolism, and apoptosis.

Promotes neurogenesis. Lithium promotes neurogenesis by stimulating growth factors and increasing neurotrophic responses. It directly impacts neurogenesis by influencing BAG-1, BCL2, BDNF, GDNF, and VEGF. Lithium has also been shown to increase synaptic plasticity and positively regulates cell survival.

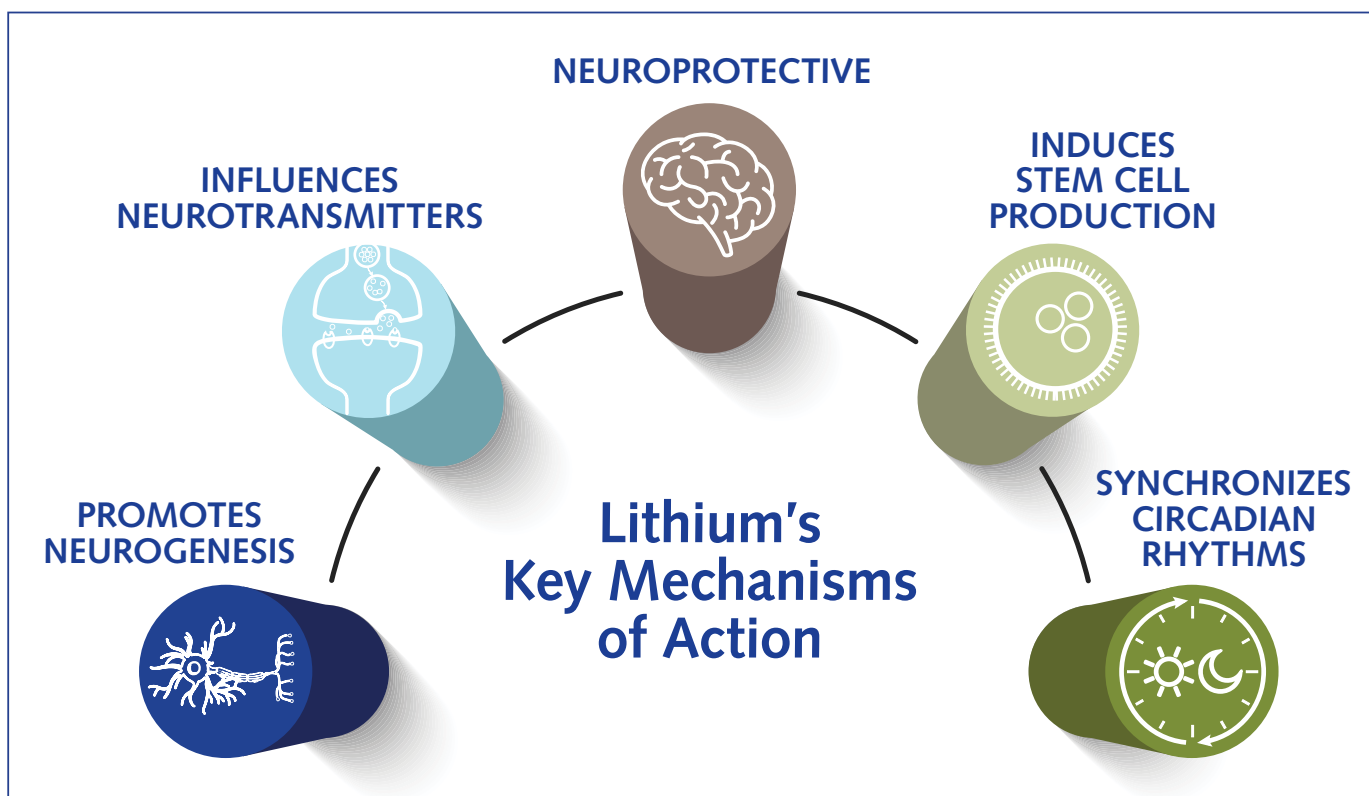
Influences neurotransmitters. Lithium modifies the synthesis and release of key neurotransmitters in the cell membrane and the entire cellular metabolism. Lithium facilitates the uptake and modulates the activity of major neurotransmitters including dopamine, serotonin, and noradrenaline. While lithium inhibits excitatory neurotransmitters such as dopamine and glutamate, it promotes GABA-mediated neurotransmission to have a calming/balancing effect.

Induces stem cell production. Undifferentiated stem cells are blank slates that have the potential to create offspring that may become neurons. Lithium has been shown to enhance the generation of stem cells from both mouse embryonic fibroblasts and human umbilical cells.

Synchronizes circadian rhythms. Lithium has been shown to modulate the expression of clock genes including ARNTL1, CLOCK, PER3, NR1D1, and TIMELESS. Because of this influence, lithium resynchronizes circadian rhythms and can help normalize hypothalamus-pituitary-adrenal axis function.

Unproven, Yet Interesting Mechanism

Lead toxicity is associated with ill health on many levels including mental health and cognition. Preliminary *in vivo* research demonstrates that lithium treatment can help mitigate lead toxicity. Brown et al's 2018 paper makes a compelling case that mitigating lead toxicity could be one way in which lithium exerts its brain health benefits. They conclude, "several lines of circumstantial evidence suggest that lithium protects against the neurotoxic effects of lead. There are significant public health implications if this paper's hypothesis is true."



Via these diverse and important pathways, we know that lithium is an essential micronutrient. It cannot be manufactured by the body, so it must be obtained through diet and/or dietary supplements.

“Like many other essential nutrients, in excess, lithium can be harmful but in low, natural amounts, it supports health,” explained functional medicine psychiatrist and nutritional lithium expert James Greenblatt, MD. “Even more important, a deficiency of lithium, just as a deficiency of other essential nutrients, can have adverse physical, neurologic, and/or psychiatric effects.”

But how common is lithium deficiency? According to Dr. Greenblatt, individuals with family histories of bipolar disorder, aggression and suicide may have higher lithium requirements.

“I routinely use trace mineral hair analysis as a means to assess a patient’s mineral status,” said Dr. Greenblatt. “After decades of doing this kind of testing, I am no longer surprised when I encounter family history of multiple suicides or bipolar disorder in individuals with undetectable lithium levels.”

Testing Lithium Levels

Lithium levels can be tested via serum or hair analysis. Blood tests are used to monitor excess circulating levels of lithium. This is important because excess lithium can have a negative impact on kidney and thyroid function. Hair analysis, on the other hand, is used to identify potential lithium deficiency. From a clinical perspective, high blood levels and low hair levels both indicate that some intervention may be necessary. If blood levels are high, lithium dosage should be lowered. And if hair levels are low, a lithium intervention should be considered.

The other reason to monitor blood levels is that some medications can increase lithium levels in the body so it’s important to continue to test serum to monitor and adjust accordingly. Some medications that can potentially increase serum lithium levels include ACE-inhibitors, diuretics, NSAIDs, and COX-2 inhibitors.

“Repeat testing and monitoring serum levels over the course of treatment is critical,” advised Dr. Greenblatt.

“I recommend that clinicians repeat testing 1 to 2 months after initiating a regimen of low-dose nutritional lithium to ensure serum lithium levels remain undetectable and that kidney and thyroid function is unchanged.”

It’s important to note that low-dose nutritional lithium should not produce measurable or detectable serum lithium levels.

Mental Health Effects

As for deficiency, some research speculates that mental health issues such as impulsivity, suicide, and even violence could be due, in part, to a lack of lithium. While no published statistics indicate how wide-spread lithium deficiency is, the scientific literature is clear that lithium can help prevent suicide and confer other mental health benefits.

In addition to the previous ecological water research, the results from a 2020 published systematic review by Del Matto et al were compelling, specifically regarding suicide prevention. The researchers evaluated 44 different studies including prospective, retrospective, and ecological with a total of more than 155,000 participants and found that even small amounts of lithium helped reduce suicide risk. They remind readers that, “The anti-suicidal actions of lithium have been consistently reported over the past 40 years, in both observational studies and RCTs [random clinical trials].”

De Matto et al’s research conclusions are consistent with Barjasteh-Askari et al who also concluded in their 2020 meta-analysis that “lithium in drinking water is dose-dependently associated with reduced suicide mortality.”

According to a 2020 clinical trial using low-dose lithium in an addiction treatment center, there was a significantly increased chance of ending the addiction cycle and self-destructive behavior with the low-dose lithium intervention versus participants who did not receive the lithium. The researchers referred to addiction as a form of “slow-motion suicide” and concluded that low-dose lithium can help improve treatment outcomes in this patient population.

Research clearly demonstrates that lithium can help with anxiety and depression, especially depression with manic episodes. This is not surprising given its direct influence on neurotransmitter activity. The myriad of other mechanisms of action illustrates why lithium can also have a positive influence on cognition.

It’s important to note that Dr. Greenblatt does not recommend low dose lithium for the treatment of bipolar disorder. Bipolar disorder is a serious, life-threatening illness and if someone is severely manic or profoundly depressed, pharmaceutical lithium can be very effective. Dr. Greenblatt is aware of many cases of

Emerging research is painting a clear picture that low-dose lithium can enhance cognition and may even help reduce the risk of Alzheimer’s and dementia.

relapse where prescription lithium was discontinued too quickly after a serious manic episode. Low dose lithium, under physician supervision, can be used for maintenance treatment after patients have been stable for at least 6 to 12 months.

Cognitive Effects

At the higher pharmaceutical doses of lithium carbonate, there can be negative cognitive ramifications including fuzzy thinking and poor concentration. However, emerging research is painting a clear picture that low-dose lithium can enhance cognition and may even help reduce the risk of Alzheimer’s and dementia.

For the past decade, the research regarding lithium’s ability to prevent cognitive decline has been growing. Leading the charge on this research has been Forlenza and colleagues who demonstrated in 2011 via their randomized controlled trial that lithium treatment was associated with a significant decrease in cerebral spinal fluid concentrations of phosphorylated-tau, an indicator of Alzheimer’s disease. Also, their research showed that in patients with mild cognitive impairment, the participants who took the low-dose lithium treatment for 1 year had better cognitive performance and attention compared to those who took the placebo.

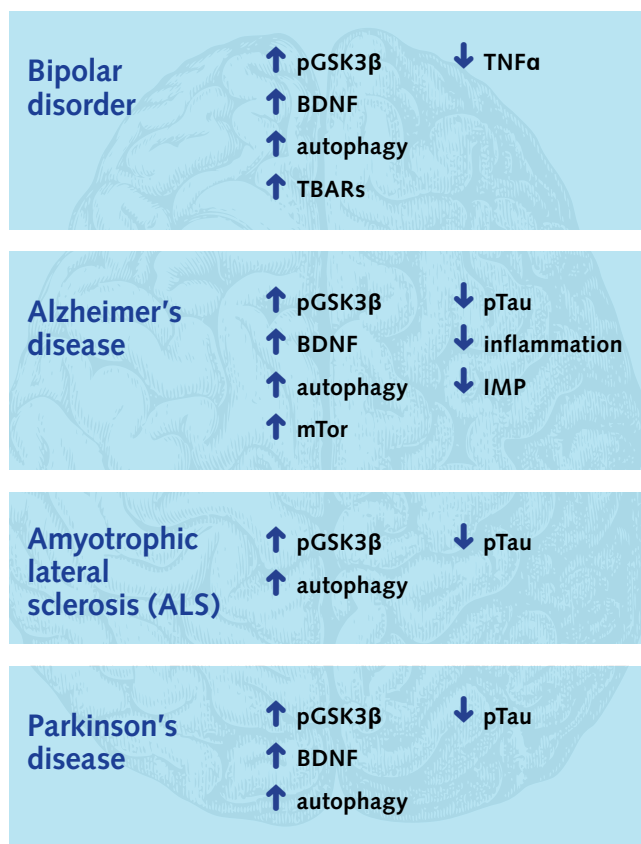
Forlenza et al followed up that research with a 2019 randomized clinical trial that also showed low-dose lithium treatment is associated with less cognitive deterioration and enhanced preservation of brain function compared to placebo in patients with mild cognitive decline, which is considered a significant risk factor for the development of Alzheimer’s. After 2 years of treatment, the lithium group outperformed the placebo group on a neuropsychological test involving memory and attention.

As mentioned previously, lithium inhibits glycogen synthase kinase activity, specifically glycogen synthase kinase-3 (GSK-3), which is a protein that helps drive memory formation. With Alzheimer's disease, GSK-3 becomes hyperactive in the hippocampus and frontal cortex where cognition and behavior are controlled. This revved-up GSK-3 activates amyloid-B and tau proteins that eventually accumulate to create the signature plaques and tangles synonymous with cognitive decline, dementia, and Alzheimer's. Because lithium can inhibit this hyper phosphorylation of GSK-3, it can help prevent amyloid plaques and tangles.

From a neuroprotective standpoint, Dwivedi et al demonstrated that damaged nerve cells exposed to lithium responded by increasing the number and length of dendritic cells. Through various means, lithium stimulates the growth and repair of neurons, which also illustrates its ability to reduce the risk of Alzheimer's.

The many neuroprotective mechanisms mean there are other important neurological applications that are surfacing in the scientific literature.

NEUROPROTECTIVE MECHANISMS OF LITHIUM



Source: Forlenza OV, De-Paula VJ, Diniz BS. Neuroprotective effects of lithium: implications for the treatment of Alzheimer's disease and related neurodegenerative disorders. *ACS Chem Neurosci*. 2014;5(6):443-450.

Other Areas of Interest

Other neurodegenerative diseases such as Parkinson's, Huntington's, and amyotrophic lateral sclerosis (ALS) may also benefit from low-dose lithium. The authors of a 2015 review state, "Lithium-only treatment may not be a suitable therapeutic for neurodegenerative diseases due to inconsistent efficacy and potential side-effects, however, the use of low doses of lithium in combination with other potential or existing therapeutic compounds may be a promising prophylactic approach to reduce symptoms and disease progression in neurodegenerative diseases."

For all of these conditions, research is preliminary but promising. Specifically, regarding ALS, *in vivo* research showed significant improvement in motor function; however, a 2010 randomized, placebo-controlled pilot study showed that combining lithium with riluzole did not slow progression.

The United States Department of Veterans Affairs is looking at the potential for lithium to help with traumatic brain injury (TBI). Their interest was sparked by *in vivo* research showing cognitive improvement after TBI. While human clinical trials are needed to confirm, the authors of a 2014 review concluded that the preliminary data demonstrated robust beneficial effects specific to TBI including "decreases in TBI-induced brain lesion, suppression of neuroinflammation, protection against blood-brain barrier disruption, normalization of behavioral deficits, and improvement of learning and memory, among others."

Another area of interest is in oncology. Once again, researchers looked to bipolar patients for some answers regarding the reduced risk of cancer. Retrospective research showed that bipolar patients taking lithium had much lower rates of cancer. A 2019 paper looking at cancer development and progression pathways compared to low-dose lithium's mechanisms of action concluded that lithium has the potential to reduce the incidence and progression of various cancers. The researchers explain that more research is needed to determine the optimal dose-response curve.

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Because of its neuroprotective effects, researchers are also looking at lithium's potential to protect the brain from the effects of cancer treatments such as chemotherapy and radiation. Often referred to as "chemo brain," cognitive difficulties can result from the treatment or the cancer itself. According to a 2012 review, while more research is needed, theoretically the proven mechanisms of action of lithium indicate it may be of some benefit in this patient population.

Practical Clinical Application

From an evolutionary perspective, we have consistently ingested small amounts of lithium from food and water since the dawn of time. Science has confirmed the concept that trace minerals originally present in our natural environments, over time, become incorporated into biologic systems that impact health. Such is the case with lithium.

"I believe there is more than enough evidence to warrant placing lithium alongside selenium, chromium, and other minerals as an essential micronutrient," concluded Dr. Greenblatt.

The influence of lithium as an essential trace mineral is complex and multilayered. Evidence is clear that low-dose nutritional lithium can help enhance mental health while reducing the risk of suicide. Research also demonstrates it can improve cognition and reduce the risk of cognitive decline, especially in high-risk individuals.

Patients likely to benefit most from low-dose lithium are those who have undetectable levels on a hair mineral analysis. Dr. Greenblatt also recommends looking for these other indicators of lithium deficiency:

- Symptoms of irritability, anxiety, aggression, compulsive, or self-injury behaviors
- Past and/or current psychiatric diagnosis of bipolar disorder, conduct disorder, oppositional defiant disorder (ODD), or disruptive mood dysregulation disorder (DMDD)
- Past and/or current substance abuse
- Past and/or current suicidal thoughts or previous suicide attempt
- Family history of mood disorder(s), suicide, or substance abuse

"I believe there is more than enough evidence to warrant placing lithium alongside selenium, chromium, and other minerals as an essential micronutrient," concluded Dr. Greenblatt.

Clinicians prescribing both nutritional or pharmaceutical lithium should be reminded to test serum lithium to ensure it is undetectable in the blood to reduce the risk of kidney or thyroid involvement.

The dosage of nutritional lithium can vary depending on many factors. Dr. Greenblatt recommends starting all patients on 1 mg of lithium and titrate doses as needed.

"It's all about biochemical individuality," said Dr. Greenblatt. "A patient's age, gender, stress level, environmental toxin exposure, diet, medications, and geographical location are all factors that need to be considered."

Based on the scientific research and clinical experience of many integrative practitioners, low-dose nutritional lithium may be a powerful adjunctive tool to help patients who are at risk of mental health issues, including irritability and poor impulse control, as well as neurodegenerative diseases.

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