# Alzheimer's Redefined:
## Nutritional Lithium as the Foundation for Prevention

**by James Greenblatt, MD**

Adapted from his book *Integrative Medicine for Alzheimer's* (Victoria, BC: FriesenPress; 2018)

In the time it has taken you to read the title of this article, someone somewhere in the world has developed dementia. Approximately 50 million people on the planet currently live with some form of this neurodegenerative disorder, and epidemiologic data reveal incidence rates to be on a meteoric rise.[1] Projections from the WHO forecast the number of cases to rise to 152 million by 2050, meaning that the global dementia burden will more than triple within the span of a single generation and leave an unprecedented population of sufferers to battle an invisible and, ultimately, lethal foe for which there is no cure.[1] Alzheimer's disease (the most common form of dementia) ranks sixth amongst the top ten leading causes of death in the US and is the only physiologic ailment amongst the top ten that cannot be remedied through pharmaceutical intervention. Attempts to find a cure for Alzheimer's and other neurodegenerative illnesses have thus far been met with stoic failure; and despite decades' worth of research and billions of dollars invested, viable solutions continue to elude the medical community.

Progressive memory loss that interferes with the tasks and activities of daily living is *not* considered to be a normal part of aging. In fact, the latest research demonstrates that the biologic processes that precipitate cognitive decline may commence decades before symptoms begin to manifest.

From one perspective, the discovery that Alzheimer's has a lengthy prodromal period is truly frightening. The knowledge that the biologic processes underlying Alzheimer's can in some be active up to four decades *before* cognitive deficits are observed adds a "Sword of Damocles-esque" facet to what is already a devastating disease. The plaques and tangles characteristic of Alzheimer's may accrue silently for years, until the day comes that the scales of neuronal health and degeneration tip irrevocably towards decline. And, as so many pharmaceutical studies have shown, once a person begins to exhibit functional cognitive deterioration, little can be done: symptomatic presentation remains a tragic point of no return for Alzheimer's sufferers and the basis for what is justifiably termed a public health crisis.

From another perspective, however, the knowledge that Alzheimer's develops slowly over a long period of time is cause for hope. A prodrome presents a window of opportunity, a chance to modify certain etiologic factors while they remain modifiable. And, as a growing body of scientific evidence suggests, many of the processes underlying Alzheimer's pathogenesis are indeed modifiable. Factors such as these are tools than can be wielded to potentially significant effect in a treatment approach centered upon *prevention* and may have the power to turn the tide in our battle against Alzheimer's and dementia. No longer must we approach neurodegenerative illness as a foregone conclusion; the newest model of disease pathogenesis offers us a chance to proactively steer neurologic aging along a course toward health.

Amidst a flurry of new research geared towards substantiating and operationalizing this new Alzheimer's prevention model, one remedy shows potential above the rest. From a long and controversial past, the mineral **lithium** has lately emerged as one of the most powerful and promising treatments available for neurodegenerative illness.

### Understanding Alzheimer's Disease

Alzheimer's is a tragic neurologic malady characterized by a progressive and irreparable shrinkage of brain tissue, which leads inevitably to declines in memory, social communication and, eventually, to death. This slow, progressive, and cumulative patterning explains why most Alzheimer's patients don't present with symptoms until over the age of sixty-five.

Pathologically, Alzheimer's is the product of two trademark lesions that occur at the cellular level: plaques and tangles. **Plaques** are formed by deposits of small protein fragments called amyloid-β (or β-amyloid) peptides, which choke the synapses through which signals are transmitted between neurons and effectively block cell-to-cell communication in certain regions of the brain. Often simultaneously, other lesions called **neurofibrillary tangles** develop within the neurons themselves. These tangles result from a disruption in the production of a different protein called **tau**. Normally, tau filaments

help to circulate nutrients and other essential supplies throughout the cell. In Alzheimer's disease, however, these strands destabilize, becoming twisted or 'tangled.' Without a functional tau system to circulate vital compounds, the neurons starve or die. The result? The cellular and intracellular processes required for the creation, storage, and retrieval of memory are disrupted, the biologic process of learning is halted, and cognition deteriorates.

There is evidence to show that plaques and tangles may actually be a common malformation in the aging human brain. New research has revealed that plaques can appear a full thirty to forty years before symptoms of cognitive decline begin to manifest.[2] A recent study published in the *Journal of the American Medical Association* presented the following statistics: ten percent of *healthy* fifty-year-olds have detectable amyloid deposits; this figure swells to thirty-three percent by age eighty, and forty percent by age ninety.[3] Individuals with a mental illness – specifically, patients with depression or bipolar disorder – are at an even greater risk of developing amyloid precursors.[4]

**Nutritional Lithium: The Unlikely Treatment**

The mineral lithium has shown tremendous promise for the treatment and prevention of Alzheimer's disease. This humble element has an extensive history of medicinal use, founded in its long-established benefits for a range of physical, emotional, and mental ailments.

By the time lithium was first isolated as a mineral salt by Swedish chemist Johan August Arfvedison in 1817, its use in traditional medicinal preparations had already spanned millennia. The Greek physician Galen (130-200 C.E.) advised patients suffering from disorders of the spirit to bathe in and drink the waters of the natural springs located in Ephesus – which, we know now, had a high lithium content. These lithium-rich mineral springs, and others throughout the world, remain and continue to be sought-after health destinations, frequented through the ages by rulers and commoners alike.

Throughout the 19th and early 20th century, lithium was used as a supplement to fortify a variety of foods and beverages. The third edition of the *Merck Index*, published in 1907, listed forty-three different medicinal preparations containing lithium[5]; the following year, the *Sears, Roebuck & Co. Catalogue* advertised Schieffelin's Effervescent Lithia Tablets for a variety of afflictions.[6] These formulations were evidently very popular, inspiring soft drink inventor Charles Leiper Grigg to create a new "lithiated" beverage in 1929. Leiper called it Bib-Label Lithiated Lemon-Lime Soda, and it was marketed for its potential to cure hangovers and lift mood.[7] This drink, better known to us today as 7-Up, contained lithium citrate until 1950.

**The more lithium in the groundwater, the healthier was the population.**

As lithium is distributed throughout the earth's crust, it is found naturally in food and water as a consequence of its presence in soil and bedrock. The US Environmental Protection Agency has estimated that the lithium intake of the average adult ranges from approximately 0.65-3.0 mg/day. Grains and vegetables are the primary sources of lithium in the standard Western diet, with animal products like eggs and milk providing the rest. As the human body cannot synthesize lithium on its own, consistent dietary intake is important. The WHO added lithium to its list of nutritionally essential trace elements in 1996, and in 2002 an article published in the *Journal of the American College of Nutrition* established a recommended daily allowance for lithium – thus cementing lithium's status as an essential mineral.[8,9]

In modern medicine, lithium is most well-known and frequently utilized for its ability to stabilize mood in individuals with affective disorders. A substantial body of strong empirical evidence, derived from research and clinical use, demonstrates that high-dose pharmaceutical lithium restores brain and nervous system function through a variety of biologic pathways. Lithium's demonstrated efficacy is such that it is considered a first-line intervention for bipolar disorder, and it is thanks to its extensive history of use for bipolar disorder that we have learned of its potential as a treatment for cognitive decline.

Researchers working with bipolar patients began to suspect that lithium may confer more than balanced mood when longitudinal and retrospective analyses revealed that subjects taking lithium displayed lower rates of dementia than did those taking other medications. In an attempt to validate this finding, one study compared Alzheimer's prevalence in sixty-six elderly bipolar patients on chronic lithium therapy with forty-eight patients who were not being treated with lithium.[10] The results were staggering: lithium therapy reduced the prevalence of Alzheimer's to levels observed in the general elderly population, with just five percent of patients in the lithium group presenting with Alzheimer's as compared to thirty-three percent in the non-lithium group. A research series conducted in Denmark explored the lithium-Alzheimer's association using differential study designs and achieved strikingly similar results: a survey of the records of over twenty-one thousand psychiatric patients revealed that lithium therapy was associated with a decreased prevalence of dementia and Alzheimer's.[11,12]

Bolstered by findings such as these, many within the scientific community were eager to explore the utility of lithium as a treatment for neurodegenerative illness in experimental settings. Unfortunately, the first clinical trials testing lithium with dementia patients proved disappointing, likely owing to the fact that researchers have thus far attempted to incorporate lithium into the same ameliorative model employed by pharmaceutical companies, i.e. testing lithium on patients who have already developed

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Alzheimer's. As pharmaceutical trials have demonstrated time and again, there is little that can be done to correct the damage to a brain in the advanced stages of neurodegenerative illness, and in this respect lithium appears to be no different.

In 2011 a team led by O.V. Forlenza turned away from standard ameliorative paradigms and instead examined lithium's potential as a prophylactic.[13] In a study designed to determine whether long-term lithium treatment could *prevent* Alzheimer's in high-risk individuals, forty-five subjects with mild cognitive impairment (MCI, a precursor to Alzheimer's) were randomized to receive lithium or placebo for twelve months. Over the course of the trial, lithium doses were maintained at sub-therapeutic levels (150-600 mg/day) to minimize the risk of potential side-effects. Analyses conducted at study conclusion revealed that subjects in the lithium group displayed a decrease in levels of tau proteins as compared to pre-trial levels. This finding came in stark contrast to that of the placebo group, in which overall tau levels rose steadily throughout the study. Equally as impressive, lithium treatment was associated with performance improvement on the cognitive subscale of the Alzheimer's Disease Assessment Scale test® and in various attentional and memory-related tasks.[14] Lithium tolerability was determined to be good as patients reported limited side effects, and the overall adherence to lithium treatment was an impressive ninety-one percent. The researchers concluded that lithium had a significant preventative impact on Alzheimer's when administered in early stages of disease pathogenesis.

### The Promise of Low-Dose Lithium

Evidence corroborating the efficacy of low-dose lithium has come primarily from epidemiologic studies in which groundwater assays have uncovered stunning correlations between lithium levels and psychiatric disorders. Between 1970 and 2013, eleven different studies involving over ten million subjects examined lithium levels in drinking water from regions around the globe and compared them to rates of suicide, violent crime, psychiatric hospital admissions, substance abuse, and overall mortality in the same locales.[15-20] Nine of the eleven studies revealed significant inverse associations between lithium and rates of adverse health outcomes; in other words, the more lithium was present in the groundwater supply, the healthier the local population was found to be.

Inspired by these incredible findings, two recent studies narrowed the scientific gaze on associations between groundwater lithium and rates of dementia and Alzheimer's. The first, a nationwide study conducted in Denmark, explored whether dementia incidence in the general population was correlated with long-term exposure to lithium in drinking water.[21] Lithium exposure was significantly different between participants who received a diagnosis of dementia or Alzheimer's during the study period (January 1, 1970 and December 31, 2013) and healthy controls: the median level of exposure for the former was determined to be 11.5µg/L, whereas the median level of exposure for controls was 12.211.5µg/L.

The second study, published in 2018 by the *Journal of Alzheimer's Disease*, examined the relationship between levels of lithium in drinking water and variance in rates of Alzheimer's mortality across Texas.[22] Lithium levels were assayed from 6,180 water samples collected from public wells since 2007, and averaged for 234 Texas counties. These levels were compared to Alzheimer's mortality rates while adjusting for a variety of environmental and physiologic risk factors (e.g. gender, air pollution, obesity, type II diabetes). Results were stunning: not only was Alzheimer's mortality significantly and inversely correlated with lithium levels, but the correlation remained significant even controlling for most risk factors. In fact, higher lithium levels were associated with lower rates of obesity and type II diabetes – both of which are independent risk factors for Alzheimer's disease.

While these findings are remarkable and have spurred global interest in the clinical applications of low-dose lithium, the transition from evidence to real-world application has been slow. As lithium is a naturally occurring mineral and cannot be patented (and is thus not profitable), financial investments into trials exploring the viability of low-dose lithium for dementia and Alzheimer's have generally been few and far between.

The magnitude of what we are all facing when it comes to Alzheimer's and dementia and the incredible, empirically corroborated potential of lithium as neuroprotective agent should trump any and all proprietary considerations, however. Additional large-scale, high-quality clinical trials using low-dose lithium are essential.

### Key Neuroprotective Mechanisms

Not only is there a significant and still-growing body of evidence demonstrating that lithium is neuroprotective, but biomolecular research has shed light onto the very mechanisms through which lithium confers its protective effects. Most significantly, lithium has been found to disrupt the key enzyme responsible for the deposition of amyloid plaques and neurofibrillary tangles – the biologic hallmarks of Alzheimer's. This enzyme is glycogen synthase kinase-3 (GSK-3), which normally plays a major role in neuronal growth and development. In the healthy brain, GSK-3 is critically important, as it helps to drive the synaptic remodeling necessary for the formation of memory.

In the Alzheimer's brain, however, GSK-3 becomes hyperactive in regions that control behavior and cognition, including the hippocampus and frontal cortex. When in such a state, GSK-3 can itself activate proteins within neurons – proteins that shouldn't be activated – such as amyloid-beta and tau. Eventually, these proteins are synthesized and activated faster than the normal processes of metabolic degradation can clear them, and they build up to form the signature plaques and tangles that disrupt brain function and result in a progressive cognitive decline. Lithium

functions as a direct GSK-3 inhibitor to prevent this overexpression, halting inappropriate amyloid production and tau activation before these proteins become problematic.[23,24]

In addition to protecting the brain from the development of plaques and tangles, lithium has been shown to repair existing neuronal damage caused by Alzheimer's. For example, lithium ions encourage the synthesis and release of key neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), which in turn stimulate neuron growth and repair.[25] Neuroimaging studies have shown that the brains of patients taking lithium have significantly higher gray matter volumes, suggesting that lithium has powerful stimulatory effects on processes relating to neurogenesis. One study has even directly demonstrated that damaged neurons exposed to lithium respond with increases in dendritic number and length.[26]

Lithium's story certainly does not end here, and we likely have only scratched the surface as far as elucidating the mechanisms through which it supports brain health. Beyond promoting neurotrophin synthesis and inhibiting GSK-3, recent studies have confirmed that lithium influences NMDA receptors, protein synthesis and modification, transcription factors, cellular autophagy and apoptosis, inflammatory mediators, glutamate excitotoxicity, microglial activation... and the list continues to grow.[27] The more we seem to learn about lithium, the more powerful the argument for its continued research and incorporation into Alzheimer's prevention strategies becomes.

**Conclusion**

As we have explored, the numbers associated with Alzheimer's disease are staggering. Countless hours, decades of research, and millions of dollars have been poured into global efforts to combat this disease; and yet we are hardly better off today than we were 10...30... even 50 years ago. While we know more about the biologic mechanisms underlying Alzheimer's than ever before, incidence rates continue to climb. Pharmaceutical companies have invested billions in the hopes of finding a cure and have little to show for it but a string of abandoned drug trials.

Instead of viewing Alzheimer's through a lens of inevitability, we can accept that Alzheimer's susceptibility lies along a continuum of risk which is dynamic *and thus alterable*. Instead of taking reactionary steps to an already-established case, we can focus our efforts on *prevention*. Instead of focusing on one singular disease pathway and trying to arrest it, we can use low-dose lithium to foster brain health through a variety of pathways.

An impressive body of scientific research confirms that lithium bestows powerful neuroprotection through a multitude of biologic mechanisms, many ➤

of which directly slow or inhibit the pathologic cellular cascades from which Alzheimer's emerges. Furthermore, it has been shown to decrease levels of existing amyloid plaques and neurofibrillary tangles which for at-risk individuals is an enormously significant discovery.

In addition to its established efficacy as a neuroprotective agent, lithium's strong safety profile makes it a particularly attractive treatment, as prevention strategies for dementia are most efficacious when initiated early and continued over a long period of time. And it doesn't take a lot of lithium: studies have shown that lithium may in fact be most effective in preventing age-related neurologic decline when used at safe, affordable micro-dose levels; studies have confirmed that doses as low as 300 µg/day exert measurable neuroprotective and cognition-enhancing effects.[28]

Low-dose lithium offers the best strategy currently available to protect the brain from the devastation of neurodegenerative disease. This strategy, in concert with a shift in focus towards prevention, offers patients and medical practitioners, worldwide, legitimate hope that the tide of Alzheimer's disease can be turned.

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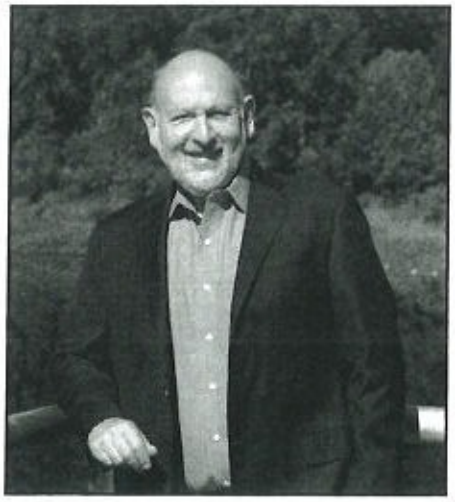


A pioneer in the field of integrative medicine, James M. Greenblatt, MD, is dually board-certified in adult and child and adolescent psychiatry with over three decades of experience treating clients with mood disorders, eating disorders, and other mental illnesses. His knowledge in the areas of biology, genetics, psychology, and nutrition as they interact in the treatment of mental illness has made him a highly sought-after speaker, and he has lectured internationally on the scientific evidence for nutritional interventions in psychiatry. Dr. Greenblatt has also published multiple books and articles for professional and consumer audiences on how to employ a comprehensive approach toward mental health treatment. His book series *Psychiatry Redefined,* which includes *Integrative Medicine for Alzheimer's* from FriesenPress, draws upon his many years of experience treating complex and diverse patient populations. Dr. Greenblatt currently offers online courses for medical and health professionals as well as specialized fellowship programs in integrative psychiatry.

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