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Ross Robison
*Ohio Northern University*

Sara Swick
*Ohio Northern University*

Lauren Bajbus
*Ohio Northern University*

Jennifer Bauer
*Ohio Northern University*

B. Shane Martin
*Ohio Northern University*

# Lithium Therapy in Alzheimer's Disease

Ross Robison, fourth-year pharmacy student from Fort Wayne, Ind.; Sara Swick, fourth-year pharmacy student from Pataskala, Ohio; Lauren Bajbus, fifth-year pharmacy student from Parma, Ohio; Jennifer Bauer, fifth-year pharmacy student from St. Marys, Pa.; B. Shane Martin, PharmD, assistant professor of pharmacy practice

**Abstract**
Alzheimer's disease (AD) is a neurodegenerative disorder with no known cure which has a strong impact on patients and their caregivers. Current treatments for AD can slow the disease progression, but cannot reverse the damage that has already been done, resulting in some level of lifelong disability for affected patients. The use of lithium has shown promising results in mice models of AD. While animal models have produced positive results, additional human trials need to be conducted in order to determine a place for lithium in Alzheimer's disease therapy. Pharmacists should be aware of this potential new use of lithium since this is a drug that requires intensive monitoring and has multiple drug interactions. By having knowledge of the rationale for using lithium in Alzheimer's disease, pharmacists can be better equipped to counsel patients and their caregivers.

## Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder which affects 2.4 to 5.1 million people in the United States, according to the National Institute on Aging.[1] AD is not a normal part of aging; rather it is a disease causing dementia characterized by a loss of cognition. This loss of cognition may be serious enough to affect a patient's activities of daily living (ADLs). AD affects the most recent memories first before progressing to other areas of the brain. Not only is AD the leading cause of dementia in the elderly in America, but it has also been tied to the deterioration of general cognitive skills.[1,2] Unfortunately, treatment of AD is limited to drugs which function only to slow the progression of the disease and abate symptoms, as there is no cure for the disease at the present time.[1] AD has been sub-classified into seven stages by the Alzheimer's Association based on the most common symptoms of the disease as it progresses. AD progression may vary greatly, and patients may not experience the same symptoms at any given stage of the disease. However, these disease stage classifications may be helpful in determining the course of action a practitioner may choose to take if a patient presents with some of the symptoms along the continuum of progressive cognitive impairment.

Stage 1: **No impairment (normal function)**
Patient experiences no memory problems and does not show signs or symptoms of dementia.

Stage 2: **Very mild cognitive decline (age-related or the earliest signs of Alzheimer's disease)**
Memory lapses, such as forgetting familiar words, are common but clinical examination does not show signs of dementia.

Stage 3: **Mild cognitive decline (early-stage Alzheimer's may be diagnosed in some individuals with these symptoms)**
Clinical examination may detect problems in concentration or memory; friends, family or co-workers may begin to notice difficulties such as problems remembering what was just read, increasing trouble organizing or difficulty performing tasks in social or work settings.

Stage 4: **Moderate cognitive decline (mild or early-stage Alzheimer's disease)**
Medical review should be able to detect clear problems in several areas such as forgetfulness of recent events, impaired ability to perform challenging mental arithmetic, forgetfulness of one's own history or becoming moody in socially or mentally challenging situations.

Stage 5: **Moderately severe cognitive decline (moderate or mid-stage Alzheimer's disease)**
Patients may need help performing ADLs and gaps in memory and thinking are noticeable. Individuals may be unable to recall their address or telephone number, become confused about where they are or what day it is, or have trouble with less challenging math, but may still remember significant details about themselves and their family.

Stage 6: **Severe cognitive decline (moderately severe or mid-stage Alzheimer's disease)**
Memory and thinking ability will continue to worsen and patients may need help with ADLs, which include use of the bathroom or dressing properly. Patients may lose awareness of their own surroundings, be able to distinguish faces of family members but not be able to remember names, experience behavioral or personality changes, or experience major changes in sleep patterns.

Stage 7: **Very severe cognitive decline (severe or late stage Alzheimer's disease)**
Individuals lose the ability to respond to their environment, carry on a conversation and eventually control movement. Patients need help with most of their daily activities and no longer recognize their closest relatives and friends.

## Etiology of Alzheimer's Disease

AD is characterized clinically by three main hallmarks which lead to decreased cholinergic neurotransmission: buildup of amyloid-β-peptides (Aβ), neurofibrillary tangles from a hy-

perphosphorylated tau protein and degeneration of cholinergic neurons.[1,3-5] Extracellular buildup of Aβ originates from the cleavage of the amyloid precursor protein (APP).[2,3] Aβ then accumulates in the brain and forms neuritic plaques which slow the brain's cognitive function by inhibiting neurologic pathways.[3,4] Alteration in synaptic function may also be due to the intracellular neurofibrillary tangles from a hyperphosphorylated tau protein, a microtubule associated protein, which misfolds and disassembles from microtubules when hyperphosphorylated. This misfolding and disassociation of the tau protein in the brain forms aggregates and therefore alters overall synaptic transmission and function.[3,6,7] Additionally, levels of brain-derived neurotrophic factor (BDNF) and mRNA are diminished in both the brain and serum of Alzheimer's patients.[6] BDNF is a neurogenerative agent which plays an important role in neuronal growth, survival and differentiation. Low levels in the body may result in neurodegeneration and a decrease in neurotrophic function. Buildup of Aβ neuritic plaques from the cleavage of APP, neurofibrillary tangles from an aggregation of disassociated tau protein and a decrease of serum BDNF have been shown to decrease the rate and efficiency of cholinergic neurotransmission.[3,4,6]

The increased expression of glycogen synthase kinase-3β (GSK-3β) is an important consideration in AD because GSK-3β has been shown to be a predominant tau-kinase in the brain and has more recently been shown to be involved with the formation of Aβ.[5,8] GSK-3β is a serine-threonine kinase responsible for phosphorylating both tau and APP, and is a necessary component of a variety of intracellular signaling pathways.[4] Over-expression of GSK-3β may cause hyperphosphorylation of tau and APP which results in aggregation of extracellular neuritic plaques as well as intracellular neurofibrillary tangles, which are both clinical markers of AD.[3,4] Due to this relationship of increased expression of GSK-3β and the major clinical markers of AD, a variety of studies have looked at the effects of dysfunctional GSK-3β on the progression and treatment of the disease by testing the inhibition of GSK-3β. Studies have shown that over-expression of GSK-3β is associated with neurodegeneration and aggregation of neurofibrillary tangles similar to AD and other dementias, making this protein a primary drug target for AD.[3-5,8]

**Lithium**

Lithium has been used in the treatment of mood disorders since 1949 and has remained first-line therapy of bipolar disorders up to present day.[5,6] It has known neuroprotective effects, but the overall mechanism is still largely unknown. It has been shown to inhibit GSK-3β both directly and indirectly which is the reason for introducing lithium into the Alzheimer's population as a possible treatment.[4,5,8] Direct inhibition of GSK-3β occurs when lithium competes with the magnesium ion for one of two magnesium binding sites on the kinase.[5] While a variety of drugs appear to have this direct inhibitory mechanism, the indirect inhibition of GSK-3β remains exclusive to lithium. The proposed mechanism of indirect inhibition is that lithium increases the N-terminal serine phosphorylation of GSK-3β, thereby allosterically inactivating the enzyme. The specific mechanism by which lithium exerts this indirect inhibition is still under investigation.

This combination of direct and indirect inhibition of the GSK-3β enzyme has been shown to protect against Aβ injury or neurotoxicity and has also been shown to reduce the amount of phosphorylated tau *in vitro* and *in vivo*.[2,5] Lithium is a complex molecule with many cellular effects, a high potential for toxicity and a narrow therapeutic range. Even levels within the narrow therapeutic range of 0.5 to 1.5 mmol/L may result in adverse effects such as diabetes insipidus, thyroid toxicity and imbalances in calcium and other electrolytes.[8] Therefore, there is a need to monitor serum levels via blood draws every four to five days during initial therapy. There are also strict dosage adjustments for patients with renal impairment because of the high potential for adverse effects.[9]

**Alzheimer's and Lithium**

It has been observed that there is a reduced prevalence of AD in bipolar patients on lithium therapy.[6] This observed correlation has recently led researchers to study the possibility of using lithium to treat Alzheimer's Disease. Mouse and cultured nerve studies have been useful in gathering significant data. However, human trials have been a little more difficult to assess and cause a number of questions to be raised upon analyzing the results.

Mice trials have helped to illustrate the effects of GSK-3β on AD. In mice, over-expression of GSK-3β induces neurodegeneration. Results showed a reduction of Aβ in the hippocampus and cortex, less neuritic aggregates, less plaque buildup and decreased glial inflammatory reactions in mice treated with lithium to inhibit GSK-3β expression compared to control mice.[3] The mice treated with lithium not only showed significant reduction in AD markers, but also showed improvement of spatial memory. This data suggests lithium may have an important role in slowing progression of AD.

Lithium has also been seen to induce BDNF production in cultured neurons and rodent models.[6] As previously stated, BDNF protects neurons from injury. In postmortem analyses of AD patients, BDNF levels were diminished in brain and serum samples. A randomized, patient-only blinded human trial was performed treating AD patients for 10 weeks with lithium. The results showed a significant increase in BDNF serum levels compared to baseline.

The *in vitro* evidence shows lithium significantly reduces AD characteristics and markers.[3,6,8] Despite the fact that studies were conducted for an appropriate length, the disease state itself has resulted in a high dropout rate making the data collected difficult to use in assessing significance. One randomized trial of 27 patients lasted 12 weeks and measured BDNF serum levels and cognitive impairment using the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) method.[6] Patients were started on lithium sulfate 42 mg twice daily and researchers used a six-week titration phase to reach targeted serum levels of 0.5 to 0.8 mmol/L. There were two dropouts in this study; one was discontinued at week eight for unknown reason beyond unwillingness to

continue, one other dropout was reported due to a serious adverse event of severe aggression and hallucinations at week seven. The results reported a statistically significant increase in BDNF serum levels and a decrease in cognitive impairment with lithium treatment compared to the placebo group. An open-label trial was conducted of 22 patients lasting longer than 12 months looking at the feasibility of using lithium in treating AD.[8] Patients were instructed to continue their daily medication regimen, but these specific medications were not documented. A specific dosing regimen for lithium was not established during the trial. Patients were started on low dose lithium carbonate 100 mg and serum levels were assessed every two weeks to reach target levels of 0.3 to 0.8 mmol/L. They started the screening process with 480 patients and excluded 458 patients for failing to meet entry screening lab levels, not wanting to participate due to frequency of assessment, compliance issues and patients with a concomitant illness or therapy that was contraindicated with lithium treatment. There were a total of 14 dropouts in this study, including two deaths unrelated to treatment. The other 12 dropouts were due to hospital admissions unrelated to treatment or relatives or investigators removing them from treatment. The authors of this trial concluded lithium was safe when dosages were kept within the therapeutic range and that side effects were mild and not the main cause of withdrawal from the study. However, with the high dropout rate and only eight patients completing the trial, these conclusions are debatable. Although there is a significant amount of literature available on this topic, more randomized, controlled human trials should be performed in AD patients even though the *in vitro* and *in vivo* studies suggest lithium may decrease the characteristics and disease progression of AD.

## Pharmacy Implications and Counseling

Since AD is a disease state of the elderly, it is important to monitor side effects, as they may be greater in the elderly population due to comorbid disease states, interactions with other drugs and a higher probability of dehydration. It is important to counsel patients on the importance of staying hydrated in order to avoid kidney stones and toxicity. Due to the narrow therapeutic range of lithium, it is important to review a patient's current medication profile and history of present illness in order to assess potential precautions. Some precautions with the use of lithium include thiazide diuretics, thyroid disease, renal impairment and heart disease.[8,9] It is also important to make sure the dosing schedule results in drug concentrations within the therapeutic range to avoid neurotoxic effects. Pharmacists and physicians also should ensure labs are being drawn as recommended in order to adjust the dose as necessary. Lithium serum level monitoring, while imperative, is a major deterrent from use since it requires frequent blood draws which may be undesirable to the patient.[9]

Lithium treatment is focused on slowing disease progression, but patients may continue to exhibit symptoms associated with AD. Health care professionals can help treat some of the symptoms of AD to make the patient more comfortable. For example, hand tremors can be treated with propranolol, while a non-thiazide or potassium sparing diuretic can be used for the adverse effects of diabetes insipidus.[1,9] Lithium has also been proven to help treat agitation and aggression associated with dementia.[7] Overall, the literature suggests lithium may be a helpful adjunct for slowing the progression of AD. When used with the appropriate therapeutic range, it may prevent progression and possibly reverse AD characteristics.

## Conclusion

There is still no cure for AD; it is a progressive neurodegenerative disorder affecting the most recent memories first and working its way to other areas of the brain. The use of lithium in slowing the progression of AD has been successful in mice studies and more research is being done to see if similar results will be seen in human trials. Researchers believe lithium to display the neuroprotective effects of inhibiting GSK-3β and inducing BDNF production; therefore, it may have the potential for use early in AD treatment. While lithium may be able to help patients with the management of AD, it is important that pharmacists check for contraindications, counsel patients on staying hydrated and help patients manage their AD symptoms to have a better overall quality of life.

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