

Is lithium a neuroprotective agent?

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BACKGROUND: Lithium was the first clinically effective mood stabilizer marketed worldwide. However, the medical literature suggests that lithium may have an indication as a neuroprotective agent.

METHODS: This review discusses the pharmacologic activity and potential effectiveness of lithium in the context of Alzheimer disease (AD) and Parkinson's disease (PD), the 2 most prominent neurodegenerative disorders in the United States. The toxicities of lithium, including lithium-induced extrapyramidal symptoms (LI-EPS) and cognitive impairments at therapeutic blood levels, are discussed. Cases that are thought to illustrate LI-EPS and cognitive impairments are critiqued.

RESULTS: Animal studies have shown positive results regarding the neuroprotective and antioxidant properties of lithium. Human studies indicate a potential benefit of lithium for improving cognition. Ongoing replicative studies are attempting to confirm the effectiveness and efficacy of lithium for treating patients diagnosed with AD or PD.

CONCLUSIONS: The available medical literature supports the conclusion that lithium should be considered as a research candidate medication for the treatment of neurologic diseases of dementias and PD.

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INTRODUCTION

Lithium is the oldest mood stabilizer indicated for treating patients diagnosed with bipolar disorder (BD). However, potential medical indications hypothesized to benefit from lithium remain to be studied in clinical trials. Lithium inhibits the enzyme glycogen synthase kinase-3 (GSK-3). This enzyme has the capability of phosphorylating and regulating substrates and

signaling cascades. It also can modulate the serotonergic and dopaminergic systems.¹ GSK-3 inhibition may be one of the primary mechanisms triggering the neuroprotection afforded by lithium. Besides GSK-3 inhibition, additional neuroprotective mechanisms include modulation of neurotrophic factors and inhibition of oxidative stress.² A complete review of the biochemical targets of lithium are extensively described by Chiu et al.³ The consensus of the literature concludes that these mechanisms may contribute to lithium's neuroprotective properties such that lithium therapy may be beneficial in treating neurodegenerative diseases.³ Still, it remains to be determined whether the effects of lithium at the cellular level are clinically relevant.

The adverse effect profile of lithium may hinder expansion of the indications of lithium to treating patients diagnosed with neurodegenerative disorders. One controversy involves the effect of lithium on dopamine (DA) function in the CNS. Long-term use of lithium has been speculated to be associated with motor disturbances that are characteristic of parkinsonism. Lithium-induced extrapyramidal side effects (LI-EPS) are theorized to stem from DA depletion in the striatum. However, to put this clinical controversy in its proper clinical perspective, in contrast to lithium, the DA antagonist antipsychotics are more likely to be associated with extrapyramidal symptoms than is lithium.⁴ Past case reports of LI-EPS often are confusing. As an example, in one case the patient's serum lithium concentration was not reported, therefore begging the question, is this a case of lithium toxicity or an adverse effect occurring from a therapeutic dose?⁵ The long-term adverse effects of lithium that include motor disturbances and LI-EPS are more likely explained as resulting from toxic serum lithium concentrations in patients with affective illness or therapeutic levels in patients being treated for indications other than affective illness, such as Alzheimer disease (AD).

Likewise, cognitive impairments induced by lithium are more commonly associated with lithium toxicity. A study by Senturk et al⁶ associated lithium with immediate verbal memory impairment in BD patients, while sparing other cognitive functions. Furthermore, in a meta-analysis, Wingo et al⁷ concluded that the data suggest that lithium treatment was associated with impairment in immediate verbal learning and memory, while sparing delayed verbal memory, visual memory, attention, executive function, and processing speed. Additionally, in healthy patients exposed to therapeutic lithium concentrations, no cogni-

tive impairment was observed.⁷ Finally, most intriguing is a clinical trial that found beneficial effects of microdose lithium (300 mcg/d) on memory among patients diagnosed with AD.⁸ Thus, the most commonly reported clinically significant CNS adverse effects resulting from lithium treatment usually are a consequence of lithium intoxication.⁹ It is a reasonable hypothesis that at current therapeutic or subtherapeutic serum concentrations, lithium would not be harmful and may benefit patients diagnosed with neurocognitive disorders. The goal of this review is to rationalize the potential use of lithium in the neurodegenerative disorders AD and Parkinson's disease (PD) by assessing its effects on memory and cognition, due to its neuroprotective and antioxidant properties.

To perform this review, a literature search was performed using MeSH terms such as *lithium*, *cognition*, *toxicities*, *Parkinson's disease*, and *Alzheimer's disease* on the PubMed and EBSCO search engines. Studies pertaining to rodents were separated from those pertaining to humans. The literature then was evaluated and incorporated into the review. Future and ongoing clinical trials also were reviewed on www.clinicaltrials.gov.

The neuroprotective and antioxidant properties of lithium

Tyrosine hydroxylase (TH). The neuroprotective and antioxidant properties of lithium have been described in several animal studies. TH, the rate-limiting enzyme in DA synthesis, serves a crucial role in DA-involved neurodegenerative diseases such as PD. When CNS concentrations of TH are decreased, DA synthesis is diminished. Consequently, it is hypothesized that increasing the TH concentration may be an effective therapy for PD.¹⁰ The toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been used in rodent models to induce PD-like symptoms and to evaluate the potential positive effects of lithium. Using a mouse model of PD, Arraf et al¹¹ demonstrated that lithium inhibited MPTP-induced depletion of DA by preventing the inactivation of TH. Furthermore, they found that although a low dose of 1.1 g/kg lithium chloride produced no significant protection against MPTP-induced PD toxicity, a 4.4 g/kg dietary dose inhibited MPTP-induced toxicity and the corresponding reduction in the TH concentration ($P < .05$).¹¹

Short-term memory impairments. The disruption of dopaminergic neurotransmission in PD can cause impairments in olfactory, motor, cognitive, and emotional functions. Some of these effects have been modeled in rodents

by administering intranasal MPTP and evaluating the induced short-term memory impairments using social recognition and step-down inhibitory avoidance tasks. Results indicated that pretreatment with lithium at a dose of 47.5 mg/kg prevented the MPTP-induced reduction in social recognition ($P < .05$). Furthermore, rats pretreated with lithium had significantly improved results on the step-down inhibitory avoidance task when compared with rats pretreated with saline ($P < .05$).¹² Therefore, at least in rodent models, it appears that lithium can positively influence cognitive function. Such findings provide insight into the potential therapeutic use of lithium in managing PD-associated cognitive symptoms.

Antioxidant activity. The antioxidant activity of lithium also may benefit PD. It is theorized that antioxidants reduce the progression of PD by preventing free radical damage of dopaminergic neurons.¹³ de Vasconcellos et al¹⁴ examined the antioxidant properties of lithium treatment using rats exposed to chronic stress. Brain biopsies of the hypothalamus and hippocampus revealed a decrease in free radical generation and an increase in antioxidant effects in the lithium-treated group.

Neurotoxin 6-hydroxydopamine (6-OHDA) is used to study PD in animal models. It causes selective and progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta. It has been proposed that lithium might inhibit the degeneration of dopaminergic neurons caused by 6-OHDA. However, using a rat model, lithium failed to protect the DA neurons from the effects of 6-OHDA.¹⁵

Alpha-synuclein protein. One of the pathologic characteristics of PD is the presence of Lewy bodies throughout various regions of the brain. Alpha-synuclein is one of the major components of Lewy bodies.¹⁶ It has been proposed that lithium may prevent the accumulation of alpha-synuclein protein. A study by Kim et al¹⁷ divided mice into 2 groups, with the experimental group receiving a diet with 0.255% lithium and the controls receiving the same diet without lithium supplementation. Lithium prevented the accumulation of oxidized alpha-synuclein proteins in multiple brain regions vs the control group ($P < .01$). The antioxidant protection that lithium afforded in this animal model suggests lithium as a potential treatment for PD.¹⁷ If lithium proves to be successful for treating PD, it also may benefit the other Lewy body-related dementias.

N-acetyl-aspartate (NAA). The neuroprotective and antioxidant effects of lithium have been demonstrated in humans. NAA is a putative neuronal marker that can

be used to detect neuronal injury in neurodegenerative diseases. Patients with AD have been found to have significantly lower concentrations of NAA in the frontal and posterior cortex. Furthermore, patients diagnosed with AD have been shown to have a 16% reduction of NAA in the hippocampus ($P < .03$). It is hypothesized that the rate of decline of the NAA concentration is linked to the progression of AD.¹⁸ Patients diagnosed with bipolar disorder also have decreased concentrations of NAA.¹⁹ Hajek et al²⁰ showed that lithium preserves CNS concentrations of NAA. Patients with BD who received lithium treatment had similar levels of NAA compared with a healthy control group. Conversely, patients with BD who were never treated with lithium had significantly lower concentrations of NAA compared with the lithium-treated patients with BD ($P < .01$) and healthy controls ($P < .05$).²⁰ The neuroprotective effect of lithium on maintaining NAA also may protect patients with BD against the development of AD. These results indicate that lithium may benefit patients at risk for multiple neurocognitive comorbidities.

GSK-3. Lithium may benefit patients diagnosed with AD because of its ability to inhibit GSK-3.²¹ This enzyme is associated with the formation of amyloid beta peptide deposits and neurofibrillary tangles via hyperphosphorylation of the tau proteins that are associated with AD.²² Hampel et al²³ treated patients diagnosed with AD with lithium, 42 mg twice daily, and titrated the dose until a lithium serum concentration of 0.5 to 0.8 mEq/L was achieved. However, the study did not find any significant decrease in GSK-3 and tau proteins in AD patients treated with lithium over the 10-week treatment course.²³ In a second trial, patients diagnosed with amnesic mild cognitive impairment (aMCI), often seen as a prodromal stage of AD, were treated initially with lithium, 150 mg/d. The dose was titrated to target a concentration range of 0.25 to 0.5 mEq/L over the course of 12 months. The aMCI patients in the control group were randomized to placebo for 12 months. Patients receiving the lithium treatment experienced a significant decrease in cerebrospinal fluid concentrations of phosphorylated tau proteins ($P = .03$). Patients administered lithium also showed stable cognitive performance and a lower conversion rate to AD.²⁴ The contradictory results between these 2 studies suggest that length of treatment and lithium dose are critical factors in designing subsequent clinical trials for determining the effectiveness and efficacy of lithium in neurodegenerative disorders. It also is possible from the conflicting results

that the lithium treatment intervention is required much earlier in the neurodegenerative process.

The clinical use of lithium in PD and dementia of the Alzheimer type

LI-EPS. A concern with using lithium for the treatment of neurodegenerative diseases is its potential to induce parkinsonian-like EPS (LI-EPS). Several case reports described what was purported to be LI-EPS. A 67-year-old woman with a serum lithium concentration of 3.6 mEq/L, approximately 4 times greater than the therapeutic level of 0.8 to 1.2 mEq/L, was admitted to the emergency department. Her signs and symptoms on admission included mental slowing, significant cognitive impairment, severe bradykinesia, severe rigidity of all 4 limbs, and postural tremor. Despite the lithium toxicity, including EPS, there were no abnormal findings in her brain tomography.²⁵

A second case described a 73-year-old male patient diagnosed with PD, who presented with deteriorating mobility and speech and difficulty in swallowing. Comorbid diagnoses included episodic depression and manic-depressive psychosis. On admission, he was taking lithium, 275 mg twice daily. Following admission, the lithium dose was increased to 1,500 to 2,000 mg/d with the antipsychotics chlorpromazine and fluphenazine added to his therapy. His condition deteriorated and his lithium level increased to 3 mEq/L. He was diagnosed with lithium toxicity, was treated with IV fluids, and the lithium was discontinued. His symptoms improved and lithium was restarted. The patient tolerated the lithium for an additional 7 years, without any additional EPS episodes causing worsening of his PD symptoms.²⁶

In a third case report, a 67-year-old male diagnosed with BD complained of resting tremor 2 months after the start of lithium therapy. Doctors were reluctant to discontinue the lithium, because the drug was controlling his mood disorder. Furthermore, it was difficult to distinguish whether the patient had LI-EPS or PD. A scan used in conjunction with an Ioflupane I231 (DaTscan) imaging agent, a PD diagnostic tool, determined that the patient had idiopathic PD rather than LI-EPS.²⁷ Although patients may experience the neurotoxic signs and symptoms within the BD therapeutic range, the likelihood of experiencing LI-EPS is greater above the upper end of the therapeutic range of 1.4 mEq/L and/or combined with other neuroleptics, as seen in these case reports. In the first case, the lithium concentration was 4 times greater than the median therapeutic range. In the second case, the patient

most likely experienced neuroleptic malignant syndrome secondary to the antipsychotics chlorpromazine and fluphenazine. In the third case, the DaTscan proved that LI-EPS was misdiagnosed.

There has been concern that lithium and antipsychotics together can cause neurocognitive damage. Cohen and Cohen²⁸ describe 4 cases involving patients taking lithium and haloperidol. These patients were characterized as experiencing severe extrapyramidal symptoms consisting of persistent dyskinesias, drug-induced parkinsonism, and delirium. The patients returned to normal when lithium and haloperidol were discontinued. Cohen and Cohen²⁸ posed the question of whether these toxic effects occurred because of lithium, haloperidol, or both. According to Cohen and Cohen,²⁸ there were no reports of such severe neurologic deficits as a result of haloperidol use. They suggested that the toxic reaction was due to the summative effects and interaction of lithium and haloperidol. However, in prospective and retrospective data collected by Juhl et al,²⁹ psychotic patients treated with both haloperidol and lithium had no signs of permanent brain damage or persistent dyskinesias. In addition, Garfinkel et al³⁰ concluded in a comparison study between haloperidol, lithium, and the combination of the 2 drugs that the combination of both medications caused no significant increase in adverse effects.

Lithium is reported to be associated with tardive dyskinesia, a late-onset extrapyramidal symptom. In one report, a 40-year-old man diagnosed with BD presented with signs and symptoms of tardive dyskinesia. He was being treated with both lithium and chlorpromazine. The patient appeared to be noncompliant with his medication. He discontinued both medications for 2 weeks, during which his dyskinesia became progressively worse. Thus, this patient's tardive dyskinesia might have been induced not by lithium, but rather, by the sensitivity of the dopamine receptors when he abruptly discontinued his regimen, ie, withdrawal dyskinesia.³¹ In a cross-sectional study by Ghadirian et al,³² patients diagnosed with BD who were being treated with lithium had a 9.2% prevalence rate of tardive dyskinesia. However, it is important to note that most of these patients also were being treated concurrently with other neuroleptic medications. Thus, it may not be lithium alone that is associated with tardive dyskinesia; rather, it is the combination of lithium and antipsychotics.³² Interestingly, in a study by van Harten et al,³³ it was proposed that lithium may have a beneficial effect by reducing the severity of tardive dyskinesia for patients taking long-term antipsychotics.

A pharmacoepidemiology study by Brandt-Christensen et al³⁴ noted that patients receiving antidepressants or lithium had an increased risk of requiring treatment with antiparkinsonian drugs. It was hypothesized that treatment with lithium or antidepressants might precipitate PD by interfering with the homeostasis of CNS neurotransmitters. The authors concluded that patients treated with antidepressants or lithium had an association between anxiety/affective disorder and PD, which in turn resulted in an increased rate of antiparkinsonian drugs being prescribed for these patients.³⁴

Lithium and cognition—negative findings. Patients taking lithium might complain of mental slowing.³⁵ However, clinically, this generally is judged to be a sign of impending lithium toxicity. Patients generally are counseled that if they sense being intoxicated, which is similar to alcohol intoxication along with GI upset, they should stop the drug immediately, go to the emergency department, and request that a lithium level be drawn immediately. Additionally, the potential of short- and long-term memory recall impairment at therapeutic serum concentrations has been proposed, although the authors suggested that, based on the sample size of 13 patients, the finding required replication.³⁶ Thus, a more robust controlled trial that assessed the effects of lithium on memory was unable to confirm the hypothesis. Ghadirian et al³⁷ contrasted the duration of lithium treatment with the degree of cognitive impairment. Patients were arbitrarily divided into either a short-term group, with lithium treatment up to 10 months, or a long-term group, with lithium treatment for >10 months. Cognitive functions were measured using the Wechsler Memory Scale and the Benton Visual Retention Test. The results indicated no evidence of memory impairment in either group.³⁷ The cognitive effects of lithium were assessed in normal volunteers. The subjects' ability to attend to and remember ongoing events was not affected.³⁸ On the contrary, additional evidence suggests lithium may benefit memory and cognitive functions. Terao et al³⁹ found that patients who had previously received or were currently receiving lithium treatment scored higher on the Mini-Mental State Examination (MMSE) than did a non-lithium treatment control group matched for age and sex.³⁹ Importantly, follow-up data noted that lithium-treated patients with BD had a lower prevalence rate (5%) of developing AD compared with the control group (33%).⁴⁰ Most recently, the evidence demonstrated that microdose lithium may decrease the rate of cognitive impairment for patients

diagnosed with AD. Using a double-blind control design, Nunes et al⁴¹ randomized patients diagnosed with AD to either lithium, 300 mcg/d, or placebo. During the 15-month-long study, the MMSE was administered every 3 months to assess cognitive functioning. The non-lithium treatment group demonstrated a significantly greater decline in their MMSE scores than did the lithium-treated group.⁴¹ These data suggest that lithium at low, nontoxic doses is not harmful for memory and cognitive functions, but in fact may reduce the risk of developing dementia.

Future research

The idea of using lithium as a therapeutic agent for the treatment of patients diagnosed with AD and PD deserves further clinical study. Clinical trials are being conducted to further investigate the effects of lithium on GSK-3 and tau protein for its protection against AD. The National Institutes of Health Clinical Center is examining the effects of lithium and divalproex on tau proteins, given that AD is associated with accumulation of tau proteins. The objective of this study was to determine whether lithium alone or in combination with divalproex will decrease tau protein concentrations in the cerebrospinal fluid of patients with AD.⁴²

The TRIANT-TE study currently is investigating the effects of lithium vs rivastigmine, an anticholinesterase inhibitor commonly used for neurocognitive affectation in PD and AD, on HIV-infected patients with neurocognitive disruption.⁴³ Additionally, preliminary data suggest that the neuroprotective and antioxidant effects of lithium may be beneficial for PD. The neuroprotective effects of lithium currently are being investigated in patients with small cell lung cancer who are undergoing radiation therapy to the brain. The study aims to demonstrate that lithium treatment prevents or lessens memory loss caused by radiation therapy.⁴⁴ If the results of this study demonstrate that lithium has a neuroprotective effect on patients diagnosed with a brain tumor, then the proposal of using lithium in neurodegenerative diseases such as PD is not far-fetched. Ideally, future research would focus on exploring the use of lithium and the outcomes it may offer for PD patients.

CONCLUSIONS

The evidence and support for using lithium for PD and AD deserves further clarification through clinical trials.

There are concerns about the toxicity of lithium, such as LI-EPS or cognitive impairments. Although these toxicities may still occur at normal lithium serum concentration levels, the risk of such toxicities have been shown to increase when lithium levels are above the usual therapeutic range of approximately 0.6 to 1.2 mEq/L. Thus, it is important to monitor the serum concentration of lithium to minimize its adverse effects and maximize its benefits. However, the data of Nunes et al⁴⁵ actually suggests that the neuroprotective effect of lithium is likely to be obvious at subtherapeutic serum concentrations. It remains to be seen from the trials what lithium concentrations patients with neurocognitive diseases can reasonably

tolerate. Several animal studies support the neuroprotective and antioxidant effects of lithium and how it may be advantageous for PD. Unfortunately, data on the benefits of lithium for patients diagnosed with PD or AD are limited. The potential role of lithium in the treatment of neurodegenerative diseases is intriguing, but until further clinical data become available, its role as a therapeutic agent remains speculative. ■

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