Lithium Trial in Alzheimer’s Disease: A Randomized, Single-Blind, Placebo-Controlled, Multicenter 10-Week Study

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Objective: Lithium, a first-line drug for the treatment of bipolar depression, has recently been shown to regulate glycogen synthase kinase-3 (GSK-3), a kinase that is involved in the phosphorylation of the tau protein. Since hyperphosphorylation of tau is a core pathological feature in Alzheimer’s disease, lithium-induced inhibition of GSK-3 activity may have therapeutic effects in Alzheimer’s disease. In the current study, we tested the effect of short-term lithium treatment in patients with Alzheimer’s disease.

Method: A total of 71 patients with mild Alzheimer’s disease (Mini-Mental State Examination score ≥ 21 and ≤ 26) were successfully randomly assigned to placebo (N = 38) or lithium treatment (N = 33) at 6 academic expert memory clinics. The 10-week treatment included a 6-week titration phase to reach the target serum level of lithium (0.5–0.8 mmol/L). The primary outcome measures were cerebrospinal fluid (CSF) levels of phosphorylated tau (p-tau) and GSK-3 activity in lymphocytes. Secondary outcome measures were CSF concentration of total tau and β-amyloid1–42 (Aβ1–42), plasma levels of Aβ1–42, Alzheimer’s Disease Assessment Scale (ADAS)-Cognitive summary scores, MMSE, and Neuropsychiatric Inventory (NPI). Patients were enrolled in the study from November 2004 to July 2005.

Results: No treatment effect on GSK-3 activity or CSF-based biomarker concentrations (P > .05) was observed. Lithium treatment did not lead to change in global cognitive performance as measured by the ADAS-Cog subscale (P = .11) or in depressive symptoms.

Conclusions: The current results do not support the notion that lithium treatment may lead to reduced hyperphosphorylation of tau protein after a short 10-week treatment in the Alzheimer’s disease target population.

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Drs Hampel and Ewers contributed equally to the study.

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Alzheimer’s disease is the most common form of dementia. Roughly 6% of persons over the age of 65 years and 35% of those over 85 are afflicted. Prognosis is poor with a mean survival time of 7–8 years after time point of diagnosis. With the proportion of elderly persons projected to increase dramatically during the next decades, Alzheimer’s disease will become an enormous public health problem. Therefore, therapeutic interventions that could even modestly delay disease onset would provide a major public health impact.

Neuropathologically, Alzheimer’s disease is characterized by an increased amount of amyloid plaques and neurofibrillary changes, including hyperphosphorylation.
of tau, paired helical filaments, neurofibrillary tangles, and neuritic plaques. Results from multiple lines of studies suggest that neurofibrillary tangles constitute a core neuropathology of Alzheimer’s disease and contribute significantly to cognitive dysfunction. Hyperphosphorylation of the microtubule-associated protein tau is hypothesized to be an essential step in the formation of paired helical filaments and neurofibrillary tangles. A key mediator of Alzheimer’s disease–related hyperphosphorylation of tau is the proline-directed glycogen synthase kinase-3 β form (GSK-3β). Postmortem studies in Alzheimer’s disease patients showed that GSK-3β phosphorylates the majority of the paired helical filament phosphorylation sites and is colocalized with tangle-bearing neurons in the Alzheimer’s disease brain. The GSK-3 α isoform plays an essential role in the production of β-amyloid (Aβ) by interacting with γ-secretase.

Preclinical studies have shown that GSK-3 activity (including both the GSK-3α and GSK-3β isoforms) can be inhibited by lithium, a longstanding drug for the treatment of primarily manic symptoms in bipolar depression. Lithium reduces GSK-3 activity in 2 ways: directly via a competition with Mg2+ and indirectly via increasing phosphorylation of the inhibitory site on GSK-3. Recent in vitro and in vivo studies showed that lithium reduced the phosphorylation of tau at Alzheimer’s disease–specific sites and blocked accumulation of Aβ in the brain. Thus, lithium may be a potential agent for therapeutic intervention in Alzheimer’s disease. Only a few studies so far have evaluated a potential effect of lithium treatment in patients with Alzheimer’s disease. Some previous studies including observational studies and case reports were suggestive of positive effects in dementia, but others reported conflicting results. However, none of these studies included randomized, placebo-controlled trials, so the results remain inconclusive.

The current multicenter study in 71 patients was randomized, placebo-controlled, and single-blind to assess the treatment effect of lithium in Alzheimer’s disease patients. The study was an effort in proof of principle rather than establishing lithium as a possible treatment for Alzheimer’s disease. We hypothesized that lithium may inhibit the GSK-3 activity and reduce Alzheimer’s disease–related abnormalities in the concentration of total tau, phosphorylated tau (p-tau), and Aβ in cerebrospinal fluid (CSF) and plasma. CSF-based measures of Aβ and tau pathology have been previously shown to be altered in Alzheimer’s disease. The current set of markers was selected since they show high accuracy for the clinical detection of Alzheimer’s disease, correlate with Alzheimer’s disease pathology in the brain, and have been proposed to be used as endpoints for the evaluation of treatment effects in Alzheimer’s disease.

**METHOD**

**Patients**

This was a randomized, single-blind, placebo-controlled, parallel-group, multicenter 10-week study. In total, 79 patients with mild Alzheimer’s disease (defined as Mini-Mental State Examination [MMSE] score ≥ 21 and ≤ 26) were enrolled at 6 academic expert memory clinics that are experienced at conducting clinical trials and research (located in Berlin, Heidelberg, Mannheim, Munich, and Tübingen). A total of 71 of 79 patients were successfully randomly assigned to either the lithium or placebo condition since 8 patients discontinued before treatment (Figure 1). The first patient was enrolled in November 2004 and the last patient in July 2005. The study was powered to detect a 25% difference between treatment groups in CSF concentration of p-tau at a power of 80% and significance level of α = .05.

Patients were diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer’s disease and fulfilled the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for primary degenerative dementia of the Alzheimer’s type. The demographic statistics of the sample are displayed in Table 1. Routine assessment involved physical, neurologic, and psychiatric examination; neuropsychological assessment using the Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog); electrocardiogram; and laboratory tests (alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, bilirubin, calcium, sodium, creatinine, osteocalcin, potassium, thyroid-stimulating hormone, thyroxine, and hematology).

Patients either were treatment-naïve or had received treatment with cholinesterase inhibitors in a stable dose for at least 6 months. Limited treatment periods with cholinesterase inhibitors were allowed, such as days or weeks, after which treatment was stopped. Antidementia comedication had been taken at a stable dose over at least 6 months in the placebo group in the form of donepezil and galantamine by 16% (n = 6) of the patients, rivastigmine by 5% (n = 2), and memantine and gingko biloba extract each by 3% (n = 1). In the lithium group, donepezil and galantamine had been taken by 11% (n = 4) and simvastatin by 6% (n = 2).

**Inclusion and Exclusion Criteria**

For inclusion in the study, patients had to fulfill each of the following criteria. Informed consent must be provided. Female patients must be without childbearing potential (postmenopausal for at least 1 year or surgically sterile). Patients’ age had to be in the range of 50 to 85 years. Clinical diagnosis of Alzheimer’s disease of mild severity
(MMSE total score $\geq 21$ and $\leq 26$) according to the criteria of primary degenerative dementia of the Alzheimer’s type and the NINCDS-ADRDA criteria for probable Alzheimer’s disease had to be present. Willingness and ability to complete all study-related procedures and to understand patient information were required of the patient. Exclusion criteria encompassed presence of abnormal values on the laboratory tests that may contraindicate treatment with lithium; untreated hypothyroidism; electrocardiogram changes indicative of cardiovascular disease; concomitant use of particular drugs (valproic acid, memantine, neuroleptics, coumarin anticoagulants, or nonsteroidal anti-inflammatory drugs); salt-restricted diet; clinically significant liver disease or elevation in alkaline phosphatase, alanine transaminase, aspartate transaminase, or total bilirubin 1.5 times the upper limit of the reference range; renal disease or creatinine elevated by 1.5 times the upper limit; drug or alcohol abuse; and participation in another drug trial within 4 weeks prior to enrollment.

**Ethics**

Ethical approval was given by the Institutional Review Board and Independent Ethics Committee of each clinical center as appropriate. Informed consent was obtained from each subject after oral and written information about the nature, purpose, and possible risks and benefits of the study was given. The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation/Good Clinical Practice.

**Study Design**

Following an enrollment visit and baseline assessments, eligible patients were randomly assigned to receive lithium sulfate or placebo (in a 1:1 ratio) and entered into a titration phase of 6 weeks. Randomization was carried out according to a computer-generated randomization list provided by AstraZeneca. Part of this list, ie, individual treatment codes, was available to the investigator since this was a single-blind study. At enrollment, patients were identified by their initials and sequentially given enrollment numbers by the investigators.
During the titration phase, there were weekly visits to adjust the lithium dose to the target serum lithium concentration of 0.5–0.8 mmol/L. The starting dose of lithium sulfate 42 mg (6 mmol Li+) was 1 + 1 tablets daily (1 tablet in the morning and 1 tablet in the evening, approximately 12 hours apart). Dosages were escalated at weekly intervals until the target serum lithium concentration of 0.5–0.8 mmol/L (measured 12 hours from last dose) was reached, with 4 + 4 tablets taken during the maintenance phase. If dose-limiting toxicity was observed, the investigator reduced the dose, using his or her clinical judgment, to a maximum tolerated dose. Also, titration was stopped if the patient had completed the maximum dose of 4 + 4 tablets daily (ie, a maximum total daily dose of 336 mg lithium sulfate). However, no dose titration was applied for placebo patients; they remained on treatment with 1 + 1 tablets daily. Drug concentration levels were assessed weekly for both lithium and placebo patients to maintain the blinding of all patients. Thereafter, a maintenance phase followed for 4 weeks (in which drug concentration levels were assessed biweekly) and end-of-treatment assessment occurred after a total of 10 weeks of treatment. A follow-up visit or telephone contact occurred approximately 2 weeks after the end-of-treatment visit. This serum lithium concentration range was in accordance with the recommendations for use in bipolar disorder and well below those levels associated with lithium toxicity.

The study was conducted in a single-blind procedure, ie, blinded to the patients and caregivers. We chose a single-blind design since the level of lithium in serum should be within a predefined range, and thus the lithium in serum was to be monitored frequently. However, serum samples for both placebo group and lithium group were obtained for keeping the blindness.

The primary outcome measures were CSF levels of p-tau and GSK-3 activity as measured by the ratio of phosphorylated cyclic adenosine monophosphate (cAMP) response element binding protein (pCREB) to total CREB in lymphocytes. Secondary outcome measures were CSF concentration of total tau and Aβ1–42, plasma levels of Aβ1–42, ADAS-Cog summary scores, MMSE, and Neuropsychiatric Inventory (NPI).

**Neuropsychological and Neuropsychiatric Assessment**

Brief assessment of disease severity was conducted through the MMSE. Global cognitive function was assessed by the ADAS-Cog. Neuropsychiatric symptoms were assessed by using the NPI.

**Cerebrospinal Fluid and Blood-Based Measures**

Cerebrospinal fluid for the measurement of biomarkers and lithium was taken at baseline and at follow-up at visit 10, ie, the end of the 10-week treatment period. Biochemical analyses were performed centrally at the Department of Disease Biology, AstraZeneca R&D, Södertälje, Sweden, except for the p-tau231 assay that was performed by Applied NeuroSolutions (Vernon Hills, Illinois). The CSF lithium assay was analyzed at the Karolinska University Laboratory, Karolinska University Hospital Solna, Stockholm, Sweden. Lithium serum concentrations were performed at the laboratories of the respective centers.

**P-tau217.** The determination of the CSF concentration of p-tau217 was performed by a commercial enzyme-linked immunosorbent assay (ELISA; Innogenetics, Ghent, Belgium, Catalog #80317). Phospho-T181-Tau determinations were performed in the range from 15.6 to 500 pg/mL.

**P-tau231 in CSF.** The determination of the CSF concentration of p-tau231 was performed by a sandwich ELISA. The calibrator used is a synthetic peptide corresponding to amino acid residues 186–236 of human tau, and concentrations are reported in peptide equivalents. Phosphorylated-tau 231 in CSF samples was determined within the concentration range between 4.88 pg/mL and 312.5 pg/mL.

**Total tau protein in CSF.** The determination of the CSF concentration of total tau was performed by a commercial ELISA (Innogenetics, Ghent, Belgium, Catalog #80323). Total tau determinations were performed in the range of 75–1200 pg/mL. Samples outside the range of determination were diluted 5 times.

**β-Amyloid (1–42) in CSF.** The determination of the CSF concentration of β-amyloid (1–42) (Aβ1–42) in CSF was performed by a commercial ELISA (Innogenetics, Ghent, Belgium, Catalog #80324). The level of Aβ1–42 was determined within the range from 73.1 to 1754 pg/mL.

**Glycogen Synthase Kinase-3 Activity in Lymphocytes**

At each occasion, 20 mL of blood was drawn into sodium heparinized tubes. Within 2 hours after the sample was taken, it was transferred to the ACCUSPIN system (Sigma-Aldrich, St. Louis, Missouri). Briefly, the anticoagulated whole blood was transferred into the ACCUSPIN tube and centrifuged at 1000 × g at room temperature (+18 to 26°C) for 10 minutes. The mononuclear band was transferred to a clean centrifuge tube and filled up with cold phosphate buffered saline and centrifuged at 250 × g at 4°C for 10 minutes. The supernatant was discarded and 5 mL MilliQ water (Millipore, Billerica, Massachusetts) was added, mixed, and filled up with phosphate buffered saline, with the last 2 steps being repeated subsequently. Sampled pellets were stored in a freezer at −80°C.

**Aβ1–42 in Plasma**

Ethylenediaminetetraacetic acid (EDTA) plasma samples (10 mL) for determination of Aβ1–42 protein levels in plasma were taken together with the CSF samples at baseline and end of treatment. The determination of the plasma concentration of Aβ1–42 was performed by a commercial ELISA (Innogenetics,
Ghent, Belgium, Catalog #80177). β-Amyloid (1-42) determinations were performed in the range of 7.81 to 500 pg/mL.

Levels of Lithium in Serum and CSF

The analysis of lithium in serum was performed at each center separately. The method for analyzing CSF lithium was based on the method for serum lithium—Lithium, LX, Colorimetry (low 0.52 mmol/L = CV 5% and high 1.37 mmol/L = CV 3.3%). The samples for measurement of serum lithium concentration were analyzed according to routine procedures at each center and the results were recorded in the case record form.

Statistical Methods

Separate analyses of covariance were used to test the effect of treatment on the change in scores between baseline and end of treatment for each outcome variable. The primary model contained the covariate baseline values to partial out any pretreatment differences in the outcome parameter, group (treatment vs placebo), weight, body mass index (BMI), and baseline blood-brain barrier function (CSF/serum albumin), with change scores between baseline and end-of-treatment as dependent variables.

RESULTS

Glycogen Synthase Kinase 3 Activity in Lymphocytes

No effect of lithium treatment on the GSK-3 activity as measured by pCREB/total CREB ratio in lymphocytes could be detected, and the mean estimated group difference in change of GSK-3 levels between lithium versus placebo was 0 (SD = 0.3; Table 2, Figure 2).

Table 2. Descriptive Statistics on Baseline and Follow-Up Biochemical Measures for Each Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline, Mean (SD)</th>
<th>End of Treatment, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CSF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-tau181, pg/mL</td>
<td>Lithium 95.58 (37.6)</td>
<td>98.84 (37.3)</td>
</tr>
<tr>
<td></td>
<td>Placebo 82.39 (28.59)</td>
<td>82.48 (29.72)</td>
</tr>
<tr>
<td>P-tau231, mmol/L</td>
<td>Lithium 85.78 (56.52)</td>
<td>91.1 (50.49)</td>
</tr>
<tr>
<td></td>
<td>Placebo 64.5 (39.2)</td>
<td>67.39 (39.39)</td>
</tr>
<tr>
<td>Total tau, pg/mL</td>
<td>Lithium 721.72 (326.29)</td>
<td>771.11 (310.48)</td>
</tr>
<tr>
<td></td>
<td>Placebo 608.43 (245.45)</td>
<td>610.18 (260.63)</td>
</tr>
<tr>
<td>Aβ1-42, pg/mL</td>
<td>Lithium 481.38 (236.62)</td>
<td>463.30 (200.78)</td>
</tr>
<tr>
<td></td>
<td>Placebo 488.92 (204.39)</td>
<td>488.85 (210.69)</td>
</tr>
<tr>
<td>Lithium in CSF, mmol/L</td>
<td>Lithium 0.1 (0.03)</td>
<td>0.31 (0.09)</td>
</tr>
<tr>
<td></td>
<td>Placebo NA NA</td>
<td></td>
</tr>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ1-42 pg/mL</td>
<td>Lithium 55.11 (33.6)</td>
<td>57.09 (29.66)</td>
</tr>
<tr>
<td></td>
<td>Placebo 83.98 (157.69)</td>
<td>99.01 (221.38)</td>
</tr>
<tr>
<td>Lithium, mmol/L</td>
<td>Lithium 0.41 (0.14)</td>
<td>0.68 (0.23)</td>
</tr>
<tr>
<td></td>
<td>Placebo 0.11 (0.09)</td>
<td>0.11 (0.09)</td>
</tr>
<tr>
<td><strong>Lymphocytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSK-3 activity</td>
<td>Lithium 9.72 (3.58)</td>
<td>9.63 (3.67)</td>
</tr>
<tr>
<td></td>
<td>Placebo 8.89 (3.44)</td>
<td>9.29 (3.7)</td>
</tr>
</tbody>
</table>

Abbreviations: CSF = cerebrospinal fluid, GSK-3 = glycogen synthase kinase 3, NA = not available, p-tau = phosphorylated tau.

The treatment effects on GSK-3 activity measured in lymphocytes that were assessed at multiple follow-up time points were assessed in mixed models for change from baseline taking the covariates mentioned previously into account. The linear models were robust against deviations from distributional assumptions, such as normally distributed residuals. In general, missing data were excluded from the analyses. With only 2 measurements, the bias was not estimable. A 2 × 2 χ² test was used to test the difference of the distribution of adverse events between the lithium and placebo groups as well as the change in number of patients with depressive symptoms across time. The significance threshold was set at α = .05. No adjustment for multiplicity of testing has been performed.
Table 3. Neuropsychological and Psychiatric Measures at Baseline and End of Treatment for Each Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE score, mean (SD)</td>
<td>23.6 (1.6)</td>
<td>22.6 (3.5)</td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>23.6 (1.7)</td>
<td>23.2 (2.7)</td>
</tr>
<tr>
<td>ADAS-Cog score, mean (SD)</td>
<td>15.6 (4.2)</td>
<td>15.6 (4.4)</td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>15.4 (5)</td>
<td>16.6 (5.1)</td>
</tr>
<tr>
<td>NPI total score, mean (SD)</td>
<td>8.9 (10.6)</td>
<td>10.9 (11.0)</td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>11.2 (11.3)</td>
<td>12.5 (9.7)</td>
</tr>
<tr>
<td>NPI depression/dysphoria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>score (yes/no)</td>
<td>13/19</td>
<td>11/18</td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>16/21</td>
<td>16/20</td>
</tr>
</tbody>
</table>

aNone of the group differences in changes of each score were statistically significant (P > .05).
bNumber of patients with presence (yes) or absence (no) of depressive or dysphoric symptoms.

Abbreviations: ADAS-Cog = Alzheimer’s Disease Assessment Scale-Cognitive subscale, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory.

Phosphorylated-Tau, Total Tau, and Aβ1–42-Related CSF or Blood

Descriptive results are displayed in Table 2. Lithium showed no statistically significant effect on any of the CSF- or blood-based measures. The difference between the lithium versus the placebo group was not significant in either p-tau181 (mean difference of change = 3.1 pg/mL, t = 0.88, df = 57, P = .38) or p-tau231 (mean difference = 0 pg/mL). Similarly, no significant difference in change of total tau between groups was found (t = 1.56, df = 57, P = 12).

Levels of Aβ1–42 in CSF were not significantly decreased within the lithium-treated group when compared to the placebo group, with the mean difference in change being −10.0 pg/mL (t = 0.6, df = 57, P = .55). When Aβ1–42 was measured in plasma, the estimated change difference for lithium versus placebo was 2.8 pg/mL (P = .81).

Cognitive and Neuropsychiatric Measures

Lithium-treated patients showed no significant improvement of performance on the ADAS-Cog compared to the control group (t = 1.65, df = 55, P = .11, Figure 3). On average, the lithium-treated group remained stable, whereas the ADAS-Cog score in the placebo group increased numerically by 1.2 points, ie, the cognitive performance declined in the placebo group (Table 3). In the lithium group, 28.6% of the patients (6/21) showed a clinically significant improvement, defined as a 4-point decrease or more from baseline, whereas 14.3% (4/28) of the subjects in the placebo condition improved. No statistically significant group differences were observed for either the MMSE or the NPI scores (t = 0.72, df = 60, P = .47 and t = 0.17, df = 60, P = .87, respectively). Presence of depressive symptoms as measured by the depression/dysphoria subscore of the NPI changed neither in the lithium group (χ² = 0.46, df = 1) nor in the placebo group (χ² = 0.92, df = 1).

Adverse Events

The frequency distribution of adverse events in the placebo and lithium groups is displayed in Table 4. A total of 28.9% (N = 11) of the patients in the placebo group and 45.5% (N = 15) of the patients in the lithium group showed no statistically significant effect on any of the CSF- or blood-based measures. The difference between the lithium versus the placebo group was not significant (t = 1.56, df = 57, P = .55). When Aβ1–42 was measured in plasma, the estimated change difference for lithium versus placebo was 2.8 pg/mL (P = .81).
FOCUS ON ALZHEIMER’S DISEASE AND RELATED DISORDERS

Lithium Levels in Serum and CSF

Serum and CSF levels of lithium are displayed in Table 2. The level of lithium in serum reached a mean (SD) of 0.68 (0.23) mmol/L at the end of treatment in the lithium group. In the placebo group, lithium levels in serum remained unchanged at the detection level (0.11 mmol/L) when the time points of 1 week after the first dose and end of treatment were compared. Lithium levels in the CSF were measured in the lithium-treated group, showing an increase from a mean of 0.1 mmol/L (SD = 0.03) at baseline to 0.31 mmol/L (SD = 0.09) at the end of treatment. The correlation between lithium levels in CSF and plasma was significant ($r = 0.75$, $P < .001$).

DISCUSSION

The major results of the current study showed that a 10-week treatment with lithium did not change the level of CSF-based markers of Alzheimer’s disease pathology, including $p$-tau, total tau, and $A_β_{1-42}$, in patients with mild Alzheimer’s disease. No significant changes in global cognitive ability as measured by the ADAS-Cog were detected. These results were observed in a group of Alzheimer’s disease patients with Alzheimer’s disease–typical abnormal alterations in total tau, $p$-tau, and $A_β_{1-42}$, suggesting that the findings apply to a representative sample of patients with Alzheimer’s disease pathology. These CSF markers were specifically chosen as the outcome measures on the basis of previous findings of the markers’ high multicenter accuracy for the diagnosis and prediction of Alzheimer’s disease, suggesting utility for the evaluation of treatment effects in Alzheimer’s disease.

We hypothesized that levels of $p$-tau may be reduced via lithium-induced inhibition of GSK-3 activity as measured by pCREB/total CREB ratio. In the current study, lithium concentrations lay within the therapeutic window of 0.5–0.8 mmol/L as recommended for the lithium-based monotherapy of bipolar disorder. The inhibitory effect of lithium on GSK-3 shown in animal models, however, was not found in Alzheimer’s disease patients in the current study. Results from a number of preclinical studies in rats and in transgenic mouse models of Alzheimer’s disease and depression demonstrated inhibition of GSK-3 activity in the brain by lithium treatment of up to 4 weeks (for review, see Gould and Manji). Such an effect was attained with serum levels of lithium within the range from 0.6 to 1.2 mmol/L, suggesting that lithium affects GSK-3 activity at human therapeutic dosages. While there was variability in the level of lithium in serum between

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Lithium (n = 33)</th>
<th>Placebo (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Post–lumbar puncture syndrome</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>6.1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

A. Lithium (n = 33) Placebo (n = 38)

<table>
<thead>
<tr>
<th>System Organ</th>
<th>Lithium (n = 33)</th>
<th>Placebo (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorder</td>
<td>5</td>
<td>15.2</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>5</td>
<td>15.2</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>3</td>
<td>9.1</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>2</td>
<td>6.1</td>
</tr>
</tbody>
</table>

B. Lithium (n = 33) Placebo (n = 38)

*Table A uses a cutoff of 4% per group.

group showed at least 1 adverse event, but this difference between the groups failed to reach significance ($P = .15$). Drug-related adverse events were significantly greater in the lithium group than in the placebo group ($P = .01$). Serious adverse events and adverse events leading to premature discontinuation did not significantly differ between the groups ($P > .05$). After randomization, terminations due to serious adverse events occurred in only 1 case (lithium treatment arm). The patient, a 74-year-old man who was excluded from the study due to a serious adverse event, showed a brain neoplasm that was recognized on a magnetic resonance imaging (MRI) scan shortly after study medication was begun. The MR scan had been acquired about one month before the start of treatment but was not available for viewing until after the treatment was begun. A second serious adverse event consisted of severe aggression with nonserious hallucination in a 75-year-old male patient 7 weeks after the start of the study. The co-medication consisted of ramipril, bisoprolol fumarate for arterial hypertension, ginkgo biloba extract for dementia, and potassium for hypopotassemia. The patient was hospitalized and released after complete recovery 17 days later. The study medication continued unchanged in this case. For the placebo condition, 1 subject who was subsequently unwilling to continue the study experienced an adverse event. One other subject experienced a serious adverse event consisting of a headache 2 days after lumbar puncture leading to temporary hospitalization and study medication. The patient recovered completely 5 days after initial occurrence of symptoms and continued the study. Adverse events leading to death did not occur in any group. The most frequent symptoms, including tremor, nausea, hypokalemia, post–lumbar puncture syndrome, headache, and hyperhidrosis, did not differ significantly between groups (Table 5A).
subjects, the mean level of lithium was > 0.56 mmol/L in week 2 and about 0.6 mmol/L for each week until the end of treatment. The lower first quartile of the distribution of lithium levels was > 0.5 mmol/L after the second week throughout the treatment, suggesting that the target level of lithium in serum (0.5–0.8 mmol/L) was met in the vast majority of treated subjects. In the current study, the lithium concentration overlapped with that in the animal studies, although in the lower half of the range. It is possible that a higher dosage of lithium might have raised the effectiveness of lithium; however, this needs to be weighed against increased potential side effects of higher dosages when applied in elderly persons.

There are only a few previous studies on the clinical effect of lithium in patients with Alzheimer’s disease, all of which are observational in nature. Results from a retrospective observational study with a large sample of patients with dementia suggested that lithium intake within 4 years prior to diagnosis is associated with increased risk of Alzheimer’s disease. However, as the authors point out, it is possible that the increased frequency of lithium intake in the Alzheimer’s disease group may be partially accounted for by the increased occurrence of depression associated with Alzheimer’s disease. A single case study reported in a patient with dementia showed that the administration of lithium alleviated symptoms of aggression and agitation, while cognition and confusion persisted even after 1.5 years of treatment. A correlative study in nondemented patients, however, found a significantly increased global cognitive ability as measured by MMSE in nondemented patients, which was associated with lithium intake, suggesting a neuroprotective effect of lithium. Due to the correlative study design and low sample size of the previous studies, however, no causative conclusion can be drawn from such results.

In addition to the effect of lithium on Alzheimer’s disease–specific pathological mechanisms, the current study evaluated the safety of lithium in patients with Alzheimer’s disease. A total of 26 of 71 subjects showed at least 1 adverse event across groups. About half of the adverse events were of mild degree and the other half of moderate degree, suggesting relatively good tolerability of lithium in Alzheimer’s disease patients. Gastrointestinal disorders were more frequent in lithium-treated patients, which is in accordance with known side effects of lithium. The 2 serious adverse events within the lithium group, including a brain tumor that was visible on an MRI taken before onset of study medication as well as a case of severe aggression, were not deemed a consequence of study medication. Thus, the current results suggest that the dosage of an average of 0.6 mmol/L is relatively safe in the patients with mild Alzheimer’s disease.

Note that the current study shows several caveats. First, we applied CSF-based measurements of Aβ and tau-related markers to assess changes within a 10-week period, including a 4-week maintenance period of the target level of lithium concentration. This observation period was chosen since animal studies had shown short-term effects in vivo on the inhibition of GSK-3 activity by administration of lithium. It is possible, however, that such a time window was too short to detect any potential changes in the generation of Aβ and p-tau. Previous clinical trials testing the effect of statins (ie, simvastatin) in Alzheimer’s disease patients demonstrated that treatment effects on CSF levels of p-tau and Aβ are detectable when assessed over a period of 3 months or 12 months. Whereas it is unknown at what rate Aβ and p-tau are released into CSF, it is possible that observation intervals longer than the current 10-week interval are required for the detection of changes in the CSF levels of such proteins. With a maintenance phase of 4 weeks at the target level of lithium, the trial duration may have been too short. Thus an effect on the CSF markers may have been visible at a longer follow-up period. It should be noted, however, that no trend of treatment-related effect on the change in the primary outcome variable of p-tau in CSF was seen at the 10-week time point.

Secondly, we assessed GSK-3 activity within the lymphocytes to assess the amount of GSK-3 activity within the brain. The relation between levels of GSK-3 as measured in the lymphocytes and cerebral levels is unknown so far. Studies in patients with schizophrenia suggest that levels of GSK-3 are reduced in the brain tissue of the prefrontal cortex when measured postmortem but it is not known whether GSK-3 protein levels were measured in the lymphocytes. Thus, GSK-3 levels may be tissue specific and GSK-3 activity levels measured within the lymphocytes may not necessarily reflect GSK-3 levels within the brain. Although GSK-3 protein levels have been detected in the CSF directly, it remains to be seen whether activity levels of GSK-3 can be sensitively assessed in CSF as well.

Note that the titration of drug dosage was implemented in the treatment group but not in the placebo group. Thus the number of tablets taken per day was eventually higher in the treatment group and may have compromised masking of the treatment condition. However, these differences in the drug application were not considered significant and may not account for the absence of an effect observed in the current study since a higher number of tablets taken is unlikely to reduce any potential treatment effect. In fact, any difference in drug application should have worked in the opposite direction, facilitating a group difference, if at all. It should be noted, also, that the major outcome variables consisted of biomarkers rather than neuropsychological measures, which should render the measurement of the treatment effect less prone to any potential blinding procedure–related biases.

In conclusion, the current results do not support the hypothesis that lithium has significant short-term effects on
cognition as well as core biologic outcome measures, such as levels of Aβ, total tau, and p-tau, in mild Alzheimer’s disease. Given the factors mentioned previously that may partially account for the absence of an effect, however, the current results may not be taken to discourage future trials on the investigation of the effect of lithium on Alzheimer’s disease. Since in transgenic mouse models of Alzheimer’s disease, the application of lithium shows reliable effects, an effect of lithium as applied in Alzheimer’s disease may depend upon how the treatment is operationalized in Alzheimer’s disease. Variability in the level of lithium in blood may have contributed to the failure to detect an effect of lithium, although we could not observe a trend for an improvement in CSF markers in a substantial portion of the subjects. Future studies may assess a potential therapeutic effect of lithium for the treatment of Alzheimer’s disease using extended treatment and observation periods with higher dose levels. A combination of lithium with other potential GSK-3 inhibiting drugs, such as valproic acid,43 may be a fruitful approach to augment the effect of lithium.43,44

Drug names: bisoprolol (Zebeta and others), donepezil (Aricept and others), galantamine ( Razadyne and others), lithium (Eskalith, Lithobid, and others), memantine (Namenda), potassium (Klotrix, Klor-Con, and others), ramipril (Altace and others), rivastigmine (Exelon and others), simvastatin (Zocor and others), valproic acid (Stavzor, Depakene, and others).

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REFERENCES


Editor’s Note: We encourage authors to submit papers for consideration as a part of our Focus on Alzheimer’s Disease and Related Disorders section. Please contact Eric M. Reiman, MD, at ereiman@psychiatrist.com.