Study Protocol

Official Title: Lithium As a Treatment to Prevent Impairment of Cognition in Elders (LATTICE)

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Scientific Background

Alzheimer's disease (**AD**) is the most common cause of dementia in adults 65 years and older.[1] AD is a terminal illness that in the run up to death leads to a complete loss of memory and independent function. Unchecked, the disease will reach epidemic proportions in the United States and worldwide by 2050, and presently, there is no intervention that has shown a clear effect on AD progression.[2] The Alzheimer's Association's 2015 trajectory report estimates that a treatment delaying onset by five years and beginning to show its effect by 2025 would decrease the total number of older Americans with AD from 8.2 to 5.2 million by 2030.[3] Additionally, a treatment that slows disease progression will also result in far fewer AD patients in the most severe stage that requires the highest level of care with the greatest cost.[3] Hence, there is an urgent need to find treatments from pre-symptomatic to symptomatic AD to meet this looming challenge. This work aims to meet this challenge.

Over the past several years, there has been increasing interest in repurposing the use of lithium for diseases involving neurodegeneration.[4] Lithium treatment has been associated with neurogenesis in the hippocampus,[5] up-regulation of important neurotrophic factors such as B-cell lymphoma 2 (**Bcl-2**) and brain-derived neurotrophic factor (**BDNF**),[6] and, relevant to this project, inhibition of glycogen synthase kinase 3 (**GSK-3**) isoforms α and β. In particular, GSK-3α interacts with gamma-secretase playing a critical role in the conversion of amyloid precursor protein (**APP**) to amyloid-beta (**Aβ**); lithium has been shown to reduce Aβ production and memory deficits in AD transgenic mouse models.[7] GSK-3β phosphorylates tau, a critical step in the formation of neurofibrillary tangles, and lithium has been shown to reduce tau phosphorylation *in vivo* and *in vitro*.[8] That lithium may alter the AD trajectory is supported by numerous observational reports showing delay of dementia onset in those treated with it.[9-13] *However, the results of the few human lithium trials conducted have been mixed.*[14-17] At this time, it is difficult to draw definitive conclusions and make recommendations for widespread use of lithium based on the current evidence as well as the unclear risk/benefit profile of lithium treatment in older adults at risk for developing AD. Research is needed to determine whether lithium has a role as an anti-dementia agent. In contrast to previous studies, we will implement an RCT with a more integrative, comprehensive approach than done before involving state-of-the-art ultra-high field (7T) human MRI, neurocognitive assessment, and blood-/CSF- based biomarker measurement to investigate the role of lithium as an anti-dementia agent.

The rate of conversion to dementia among older adults with mild cognitive impairment (**MCI**) is 15% per year in clinic samples.[18] Accordingly, we will enroll older adults who meet criteria for MCI in which we will assess whether lithium can alter the AD trajectory.[19] Enrolling individuals who exhibit no cognitive impairment would be the basis of a different, much larger and longer study given the lower rates of AD conversion compared with individuals with MCI. Conversely, enrolling individuals with established AD is likely too far in the disease process for lithium to make a significant difference.

Study Objectives

Specific Aim: To examine the potential disease modifying properties of lithium in individuals with MCI in delaying conversion to dementia.

H1: a) Participants randomized to take lithium for two years, compared to placebo, will better maintain cognitive function, primarily in memory, which b) will be associated with changes in biomarkers (e.g., GSK-3β activity, BDNF).

H2: a) Participants randomized to take lithium for two years, compared to placebo, will have larger hippocampal volumes and lower total gray matter thinning, which b) will be associated with changes in biomarkers (e.g., GSK-3β activity, BDNF) and c) better cognitive function, primarily in memory.

Exploratory Aim: To examine whether lithium is related to additional markers of enhanced brain integrity (e.g., lower level of microbleeds, higher white matter integrity, better network connectivity, or decreased CSF phospho tau levels).

Study Design & Methods

Enroll and randomly assign 80 individuals 60 years and older with MCI to take lithium, titrated as tolerated to a blood level of 0.6 to 0.8 mEq/L, or placebo for two years to assess lithium's effects on preserving cognition and delaying conversion to dementia. Participants will receive annual neurocognitive assessment, ultra-high field (7T) brain MRI (e.g., high-resolution imaging of hippocampal and total cortical gray volumes, white matter integrity, dynamic imaging), blood- (e.g., GSK-3β, BDNF, cytokines) and CSF-based (e.g., Aβ, total tau, and phospho tau) biomarker measurement. All subjects will undergo baseline PET imaging of Aβ on which to stratify randomization. *This study is powered to detect medium/large effect sizes for H1-2, and will serve as the "go/no-go" for a subsequent, larger-scale, confirmatory study*.

Eligibility Criteria

Inclusion criteria:
1. 60 years or older
2. Diagnosis of Mild Cognitive Impairment

Exclusion criteria:
1. Major psychiatric illness (mild psychiatric illness may be included)
2. Major neurologic illness (e.g., multiple sclerosis)
3. Contraindication to lithium (e.g., renal insufficiency)
4. Unable to complete neuropsychological testing due to non-remediable impairment (e.g., blindness)

Statistical Considerations

HYPOTHESIS TESTING. All statistical analyses will be conducted starting with basic descriptive techniques and two sample testing (t-tests, Wilcoxon tests, chi-square tests) for testing the difference between the intervention and control groups. Statistical tests will be two-sided and interpreted at the 0.05 level. We have also performed all of our power computations and have provided effect sizes for all adjusted analysis ($p<0.01$) due to multiple testing. Additionally, all of our voxel-wise analyses results will be corrected using FWE. These analyses will then inform the next step in the analysis process that will include statistical modeling. First, adherence will be assessed over time by intervention group using a Kaplan-Meier approach where non-adherence is considered to be an "event." For all modeling, we will use regression diagnostics to identify potential outliers or influential observations. Additionally, the analyses will be assessed for the impact of missing data. For the initial reporting of all results, we will follow the guidelines outlined in the CONSORT statement and follow intention to treat principles: subjects will continue to be followed and analyzed according to the original randomized assignment.[134, 135] Tests of whether missingness is at random will be performed. Should missing data prove to be an issue, we will rely on inverse probability weighting or imputation as part of the analysis.

Specific Aim: H1-2. This analysis focuses on assessing the effect of lithium on: (H1) cognitive performance and, (H2) neuroimaging measures of hippocampal volumes and total gray matter and cognition. Outcomes are measured at three time points, and our primary analysis will consist of linear mixed effects models. These models will include a term for time, group and a time-by-group interaction. We will test for lithium effect by testing the significance of the coefficient associated with the interaction term in the model as well as by a likelihood ratio test between the models with and without interaction. First, we will fit these basic models for each of the outcomes of interest and test for the time-by-group interaction as an assessment of the effect of lithium. Second, we will include potential covariates (e.g., age, education, sex, etc.) and exploratory covariates (e.g., physical activity) that may influence the group effect and test for a time-by-group interaction in this context. We will examine the biomarker trajectories across the two groups. If the assays used to measure the biomarkers produce results outside of the detectable limits, we will use tobit model and mixed model extensions of the tobit model to test for differences between the two groups.

POWER ANALYSIS. For H1a/H2a, where 80 subjects will be randomized to one of two groups with 64 completers (32 in each cell), we computed power based on the following assumptions: a two-sided significance level of 0.05, a power of 0.80 and measurements at three time points for a repeated measures model. Based on these assumptions, we are powered to observe an effect size (Cohen's **d**) of 0.57 (i.e., medium) when the observations are correlated at a level of 0.5 across time. The effect size ranges from 0.45 to 0.60, a little over a half standard deviation difference in the outcome variable, as the correlation between repeated observations ranges from 0.1 to 0.6. We also computed the effect size for a two-sided significance level of 0.01, *a more conservative alpha for testing multiple outcomes*, and power of 0.80 as above and found that the effect size ranged from 0.54 to 0.72 as the correlation between repeated observations ranged from 0.1 to 0.6.

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