Published in final edited form as:

Contemp Clin Trials. 2018 August ; 71: 33–39. doi:10.1016/j.cct.2018.05.019.

Lithium Treatment for Agitation in Alzheimer's disease (Lit-AD): Clinical rationale and study design

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Abstract

Symptoms of agitation, aggression, and psychosis frequently occur in patients with Alzheimer's disease (AD). These symptoms are distressing to patients and caregivers, often lead to institutionalization, are associated with increased mortality, and are very difficult to treat. Lithium is an established treatment for bipolar and other psychotic disorders in which agitation can occur.

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Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02129348) Identifier NCT02129348

Contributors

DPD conceived and designed the study. NIA sponsored the trial. DPD is the principal investigator at the Department of Psychiatry, New York State Psychiatric Institute and Columbia University Medical Center. EAC is the principal investigator at the Department of Psychiatry, University of Miami Miller School of Medicine site. BF is the principal investigator at McLean Hospital site. MH is the principal investigator at the Department of Psychiatry, University of Texas Southwestern Medical Center site. GHP and EDH were the sub-investigators. HA contributed to database development and strategy, and JGS contributed to recruitment. DPD and JGS drafted the manuscript. All authors have read and approved the final version of the manuscript.

Ethics Approval

The study has been approved by: the New York State Psychiatric Institute Institutional Review Board, the University of Miami Miller School of Medicine Institutional Review Board, the Partners Health Institutional Review Board, and the University of Texas Southwestern Institutional Review Board. The study is registered at [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02129348) (NCT02129348) and will be carried out under the surveillance of the four institutional Review Boards and the study Data Safety Monitoring Board.

The Lit-AD study is the first randomized, double-blind, placebo-controlled trial to assess the efficacy of lithium treatment for symptoms of agitation or aggression, with or without psychosis, in older adults diagnosed with AD. Patients are randomly assigned to low dose (150–600 mg) lithium or placebo, targeting a blood level of 0.2–0.6 mmol/L, stratified by the presence/absence of psychotic symptoms. The study duration for each patient is 12 weeks. The primary study outcome is change in the agitation/aggression domain score on the Neuropsychiatric Inventory (NPI) over the study period. The secondary outcome is improvement in neuropsychiatric symptoms defined as a 30% decrease in a NPI core score that combines agitation/aggression and psychosis domain scores. The Treatment Emergent Symptom Scale (TESS) is used to assess somatic side effects. Other exploratory analyses examine the associations between improvement on lithium and indices shown to be associated with response to lithium in bipolar disorder: serum brain-derived neurotrophic factor (BDNF) levels, a SNP in intron 1 of the ACCN1 gene, and variation at the 7q11.2 gene locus. If lithium demonstrates efficacy in this Phase II pilot trial, a Phase III study will be developed to establish its clinical utility in these patients.

Keywords

Alzheimer's disease; lithium; agitation; aggression; psychosis; aging

INTRODUCTION

Symptoms of agitation, aggression, and psychosis commonly occur in patients with Alzheimer's disease (AD).^{1,2} These symptoms are distressing to patients and caregivers, difficult to treat, and are associated with accelerated disease progression, increased risk of institutionalization, and mortality.³ In a meta-analysis, caregiver education and behavior modification studies revealed a small to medium effect size in treating agitation in these patients.⁴ These studies, however, were not double-blind and lacked an adequate control group for comparison, biasing the results toward the active behavioral intervention. Consensus statements acknowledge that the value of behavioral strategies is limited in patients with severe agitation and psychosis, and pharmacological treatment is typically needed.^{4, 5}

There is no FDA-approved treatment for agitation in patients with AD. Among psychotropic medications studied in AD, antipsychotics are the only class that has consistently demonstrated efficacy in randomized, double-blind, placebo-controlled trials to treat agitation and psychosis. Antipsychotics are, however, associated with several, often severe, side effects and carry a black box warning for increased mortality in patients with dementia. In AD, lithium has been studied for its putative cognitive enhancing effects with equivocal results^{6, 7, 8}; patients with psychosis or agitation were typically excluded from these studies. In these studies targeted to treat the cognitive decline in patients with AD, low oral doses of lithium with blood levels in the 0.2–0.8 mmol/L range were associated with few to no side effects.^{6, 7, 8, 9} There have also been a few negative case reports that found lithium ineffective for treatment of behavior problems in dementia¹⁰ with possible lithium-induced extrapyramidal effects in patients with Alzheimer's disease¹¹. These were not double-blind placebo controlled studies.

Lithium is an established treatment for bipolar and other psychotic disorders in which the symptom of agitation is common.^{12, 13} There have been no systematic placebo-controlled trials of lithium to treat agitation or other neuropsychiatric syndromes in AD or other types of dementia. In case reports that targeted lithium serum levels of 0.6-1.6 mmol/l to treat both cognition and behavior in AD, adverse effects were common at higher serum levels within this range.¹⁴ An NIH-sponsored trial of lithium using a relatively high serum level of 0.4-1.2 mmol/L for the treatment of the FTD spectrum tauopathies, Progressive Supranuclear Palsy and Corticobasal Degeneration, was begun (NCT00703677), but stopped due to poor tolerability, including increased falls.¹⁵ Our initial open label case series in three patients with AD and three patients with frontotemporal dementia (FTD) suggested that low-dose lithium may be effective in the treatment of agitation and related symptoms.¹⁶ In that series, several patients who showed no response or partial response to antipsychotics improved on lithium as determined by clinical judgement and/or objective rating scales, and side effects were absent to tolerable at low oral doses (300 – 600 mg) with low serum levels at the final visit (0.30-0.32 mmol/L). These initial pilot experiences led us to develop the Lit-AD trial, which is a randomized, double-blind, placebo-controlled low-dose lithium treatment trial for agitation with or without psychosis in patients diagnosed clinically with AD.

METHODS

Study Design Features and Rationale

The plan is to recruit eighty patients clinically diagnosed with Alzheimer's disease and who manifest symptoms of agitation. There are four sites: New York State Psychiatric Institute/Columbia University Medical Center in New York, NY (NYSPI/CU, lead coordinating site); University of Miami Miller School of Medicine, Miami, FL (UM); McLean Hospital, Harvard University, Belmont, Massachusetts; and the University of Texas Southwestern Medical Center, Dallas TX. Patients are randomized to lithium or placebo with the presence/absence of psychosis as the stratification factor, and followed for 12 weeks in the trial.

Recruitment, Eligibility, Consent

NYSPI/Columbia Recruitment—The Memory Disorders Center (MDC) at New York State Psychiatric Institute and the Behavioral Neurologists' practice group at New York Presbyterian Hospital, both of which are local sites for the Columbia University Alzheimer's Disease Research Center, are the main sources of recruitment. Newspaper advertising is also used to increase recruitment.

University of Miami Recruitment—Patients are recruited from the UM Memory Disorders Clinic patient caseload of the UM investigators, and referrals from both the Department of Neurology and Family Medicine.

McLean Hospital Recruitment—Patients are recruited from the Memory Disorders Clinic, patient caseload of the investigators, and referrals from community psychiatrists and neurologists.

University of Texas Southwestern Recruitment—The Parkland Hospital Geriatric Psychiatry clinic is the main source of recruitment, supplemented by referrals from the Memory Disorders Clinic.

Inclusion/Exclusion Criteria

Salient inclusion criteria are a diagnosis of possible or probable Alzheimer's disease by NIA criteria^{17,18} based on all available clinical and laboratory information, score ≥ 4 on the NPI domain score for agitation/aggression, Folstein Mini Mental State Exam (MMSE) 5–26 inclusive, and availability of an informant. Patients with a history of bipolar disorder or other psychotic disorder prior to the onset of dementia, or specific neurological disorders, are excluded. Detailed inclusion/exclusion criteria are described in Table 1.

Agitation/Aggression and Psychosis criteria—Agitation/Aggression is assessed by the NPI agitation/aggression subscale. On this subscale, a score ≥ 4 (frequency $\times$ severity, range 0 to 12) indicates moderate to severe symptoms, and this is required for study inclusion. Psychosis is assessed with the NPI delusions and hallucinations subscales. The presence of psychotic symptoms is defined as either NPI delusions or hallucinations subscale score ≥ 4 .

Length of Clinical Trial

We chose 12 weeks as our study period in order to achieve safe dose titration with sufficient time to observe change in symptoms and the possible occurrence of side effects. A longer duration would have risked an increase in dropouts as well as clinical and ethical issues for these difficult-to-treat patients.

Treatment Regimen

An estimated eighty patients will be recruited to the double-blind treatment trial, with patients randomized 1:1 to each of the two treatment groups (lithium arm and placebo arm). The randomization is carried out by the statistician and implemented by the pharmacist, with individuals stratified by the presence/absence of psychosis as determined by an NPI domain score ≥ 4 on either delusions or hallucinations. The randomization sequences are balanced in blocks of four in this four-site study. Using a larger block size could lead to considerable imbalance between drug and placebo assignment in sites with low recruitment, and we wished to avoid that possibility.

At baseline (week 0) patients are randomized to lithium carbonate 150 mg or placebo. At the week 2 visit, blood is drawn for serum lithium level and the oral dose subsequently adjusted from 150 mg daily up to 300 mg daily if needed, based on clinical response, side effects and lithium level (real or sham). Study physicians target serum lithium levels of 0.2–0.6 mmol/l, which is lower than the therapeutic range recommended for adults with bipolar disorder.¹⁹ Clinical response in symptoms and side effects are primary in guiding oral lithium dose adjustment, aided by information obtained from serum/sham lithium levels. Based on these clinical and serum lithium level inputs, the same procedures for dose adjustment are completed at subsequent clinic visits with the dose range increasing at week 4 (150 mg – 450 mg), and week 6 (150 mg – 600 mg), with a maximum lithium daily dose of 600 mg

daily prescribed at week 6 or subsequent visits as needed. Week 10 is a phone interview but in-clinic visits can occur instead at week 10 if the patient is not medically stable or an additional lithium serum level is needed for oral dose stabilization. The week 12 visit includes comprehensive evaluation and assessment and concludes the double-blind study period. At week 12 or end- study visit in case of early dropout, a physician independent of the research team breaks the blind to the patient and informant, and follows the patient in a flexible open-label treatment period that can extend to another 12 weeks if needed. Study physicians remain blind to lithium/placebo assignment for the entire study.

Blinded Lithium Levels Procedure

These procedures are based on those used in placebo-controlled trials of lithium in mood disorders.²⁰ A physician independent of the study has the patient assignment list, and receives the serum lithium levels from the local laboratory using standard procedures. This physician then provides the actual lithium level to the study physician for patients randomized to lithium, and makes up a comparable “sham” level for patients on placebo. These unblinded, independent physicians (one at each site) are provided with each patient’s current daily oral dose of blinded study medication and the number of hours between the last oral dose and blood draw to assist them in making up a convincing, comparable sham level. The unblinded physician uses the actual lithium levels of patients who are on active lithium as a guideline to generate sham levels in patients assigned to placebo with the same daily doses and similar hours since the last oral dose.

Specific Aims and Hypotheses

Specific aim 1—To compare changes in agitation/aggression with or without psychosis in patients with AD who receive 12 weeks of randomized, double-blind treatment with lithium or placebo. Hypothesis 1: Over 12 weeks, the agitation/aggression domain score on the NPI will decrease significantly more in the lithium group than in the placebo group. Hypothesis 2: Over 12 weeks, the proportion of responders on lithium will be significantly greater than the proportion of responders on placebo. Response is defined as a 30% decrease in NPI core score (defined as the sum of domains for agitation/aggression, delusions, and hallucinations) with a Clinical Global Impression (CGI) change score of much improved or very much improved (CGI based on behavioral symptoms only). Exploratory hypothesis: Over these 12 weeks the psychosis score, measured by the sum of the NPI domain scores for delusions and hallucinations, will decrease significantly more on lithium than placebo.

Specific aim 2—To evaluate the tolerability of low dose lithium by assessing emergent somatic side effects over the course of the 12-week trial on lithium compared to placebo.

Specific aim 3—To explore associations between improvement on lithium (decrease in agitation/aggression and psychosis scores) and serum brain-derived neurotrophic factor (BDNF) levels obtained at baseline and 12 weeks), a SNP in intron 1 of the ACCN1 gene, and variation at the 7q11.2 gene locus, because these indices are associated with lithium response in bipolar disorder.^{21, 22, 23}

Study Measures

Study measures with time-points of administration are listed in Table 2. At each visit, the study physician administers the NPI and Clinical Global Impression (CGI). The research technician documents the number of caregiver communications (Frequency of Contact form) with the research team, excluding contacts to change appointments, as an index of caregiver distress; this is a simple, novel measure. The Zarit Caregiver Burden Interview and the NPI caregiver distress rating for each NPI domain are also assessed.

Extensive neuropsychological testing typically is not possible in a large proportion of these patients with moderate to severe dementia and symptoms of agitation. The Mini Mental Status Examination (MMSE) is given at screening and week 12, using two different versions of the three-word recall item to reduce practice effects. The Severe Impairment Battery (SIB) is given at baseline and week 12.

Tolerability is evaluated by assessing emergent somatic side effects using the Treatment Emergent Symptom Scale (TESS), and by the evaluation of Serious Adverse Events (SAEs) and Adverse Events (AEs).

The Katz Basic Activities of Daily Living (BADL) Scale is completed by the patient's informant. This scale was chosen because most patients participating in treatment trials of agitation in AD have moderate to severe dementia and basic activities of daily living are often impaired.^{24, 25, 26}

As described under exploratory hypotheses, blood is drawn to determine serum brain-derived neurotrophic factor (BDNF) levels, the SNP rs11869731 in intron 1 of the ACCN1 gene, and the number of VNTRs at the 7q11.2 gene locus (D7S1816).

Clinical Evaluation

History includes the chief complaint, diagnoses, referral source, age, age-at-onset of Alzheimer's disease, education, medical history, and medications used. Cerebrovascular risk factors are assessed: hypertension, ischemic and other cardiovascular disease, diabetes mellitus, smoking, family history of heart disease and stroke, TIAs, and hyperlipidemia. Alcohol/substance use, head injury, thyroid disease, other medical conditions, surgery, and hospitalization are also assessed. Family history of dementia and psychiatric diagnoses are obtained from informant interview and medical records.

Physician Evaluation

At baseline, the study physician completes a neurological and psychiatric evaluation. Complete blood count, thyroid, renal, and liver function tests, cholesterol and triglycerides, serum folate, B12, urinalysis and ECG are obtained. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G), documenting medical burden in the major organ systems each on a 4-point anchored rating scale, is completed at baseline.

Genetic Testing

Apolipoprotein E (apo E) genetic analysis on a blood sample is done through the laboratory of the Human Genetics Resources Core (HGRC) at Columbia University Medical Center. Genetic samples from this study will be genotyped by the LGC Genomics Group (Beverly, MA, USA) using their KASP genotyping assay. This method is based on competitive allele-specific PCR and enables bi-allelic scoring of single nucleotide polymorphisms (SNPs) and insertions and deletions at specific loci. PCR amplification, driven by specific-tail fluorescence labelled primers, allows the precise characterization of each SNP.

Results of apo E genotyping are not released to the patient, as indicated in the informed consent form. Further, DNA extracted from this sample will be analyzed at Columbia University using the matrix-assisted laser desorption/ionization (MALDI) time-of-flight (TOF) mass spectrometry (MS) based MassARRAY platform (Sequenom MassARRAY MALDI-TOF) for the ACCN1 gene (SNP rs11869731 located in intron 1) and the 7q.11.2 gene locus.^{21, 22}

In a genetic study of 52 patients with bipolar disorder, several SNPs were nominally associated with lithium response.²¹ The strongest association, also supported by the quantitative trait analysis, was shown with the minor G allele (allele frequency=10.3% in control populations) of a SNP (rs11869731) located in intron 1 of the ACCN1 gene.

In another study, in a complete genome scan using 378 markers spaced at an average distance of 10 cM in patients with bipolar disorder treated with lithium, a locus on chromosome 15q14 seemed to be implicated in the etiology of bipolar disorder, whereas the number of variable number tandem repeats (VNTRs) at the 7q11.2 locus (84cM) was related to lithium response.²²

Brain Derived Neurotrophic Factor (BDNF) Testing

Blood is drawn for serum BDNF assays at baseline and at the end of the trial. In exploratory analyses, change over time in BDNF levels will be correlated with change in NPI agitation/aggression and psychosis scores on lithium compared to placebo.

Serum samples are prepared by allowing whole blood to coagulate for 30 minutes at room temperature and then centrifuged at 1000×g for 10 minutes. The supernatant serum is then placed in a cryostat tube and rapidly frozen and stored at -80°C until assayed. Analysis of BDNF concentrations in the serum is performed using the Chemikine BDNF Sandwich ELISA Kit EMD MILLIPORE, St Charles MO. The samples and standards are diluted in a diluents buffer and the assays performed in 96 well plates. Absorbance is measured at 450 nm using a Spectra Max Plus 190 plate reader (Molecular Devices, Sunnyvale, CA). Measurements are performed in duplicate, averaged to give a value in pg/ml which is then expressed as ng/ml after dilution correction. Intra and inter-assay CV% are <6% and <12% respectively.

In 27 patients with mild AD (not selected for psychosis or agitation) treated with lithium at one site in a multi-center study⁶, a significant increase in BDNF serum levels, and a corresponding significant decrease of ADAS-Cog sum scores in comparison to placebo-

treated patients, was reported.²³ We will explore baseline serum BDNF levels as a potential baseline predictor of lithium treatment response, and increase from pre to post-treatment BDNF levels as a potential biomarker correlate of improvement in symptoms.

Concomitant Medications

The use of putative cognitive enhancers, narcotics, all classes of psychotropic medications, and over 20 other classes of commonly prescribed and over the counter (and alternative) medications is documented in a rating form at baseline and at the week 12 visit. An exclusion criterion is daily use of medications known to have adverse renal effects in combination with lithium, including the diuretics hydrochlorothiazide at a dose greater than 25 mg daily or furosemide greater than 10 mg daily. Whenever possible, patients receiving concomitant antidepressants or antipsychotics or benzodiazepines (dose 1 mg daily) are washed off these medications for at least 24 hours before starting the clinical trial. Patients or caregivers who do not wish to discontinue antipsychotics or antidepressants are allowed to enter the trial provided there is no contraindication to concomitant lithium use with that specific psychotropic medication. All concomitant psychotropic medications are maintained at a stable dose during the 12 week trial. During the trial, patients are permitted to receive lorazepam as needed up to 1.0 mg per day as rescue medication.

Thyroid and renal functions

Long-term use of lithium, typically over several decades, can lead to thyroid hormone deficiency.²⁶ Patients with impaired thyroid function tests are not eligible, but patients with treated hypothyroidism and normal thyroid function tests are eligible (Table 1).

End-stage renal disease is a rare complication of long-term lithium treatment and affects 1% of patients who have taken lithium for 15 years or longer. Lithium should not be prescribed for patients with serum creatinine levels higher than 1.5 mg/100 ml, and this criterion is used in Lit-AD (Table 1).^{27, 28, 29} For Glomerular Filtration Rate (GFR), values less than 60 ml/min/1.73m², with an adjusted threshold for African-Americans, typically are read as abnormal. However, in individuals over 70 years of age, approximately 50% have an abnormal GFR because of a required age adjustment in the standard GFR calculation.³⁰ For this short-term Lit-AD trial, based on literature review and consultation with a nephrologist that served as the basis for IRB review and approval, a GFR exclusion criterion of less than 44 ml/min/1.73m² was chosen for this sample of elderly patients while maintaining the exclusion criterion of creatinine 1.5 mg/100 ml. Renal function is tested at screening, week 6, and week 12. If renal function worsens to the point that the patient meets the creatinine or eGFR study exclusion criteria, the patient will be terminated from the trial for reasons of safety.

Informed Consent and Ethical Aspects

Many patients with AD do not retain the capacity to consent to research. Lit-AD patients are required to either have the capacity to provide informed consent and sign the IRB-approved informed consent form, or to have the capacity to appoint a surrogate decision maker, or provide assent for a caregiver to sign the informed consent form on their behalf, depending on local regulations that are followed at each site. The U.S. FDA has certified by letter that

this study, funded by the National Institute on Aging at the NIH, does not require an Investigational New Drug (IND) application.

The informed consent form states that the information provided by the subject will be kept strictly confidential, with access limited to the research staff with the exception of State of Federal regulatory personnel for audits. Each subject is given a code number and the patient's name does not reside in the computerized master database which is password protected and behind a departmental and institutional firewall. The research coordinator at each site enters the data directly into the electronic database with systematic double-checks before and after data entry. The research data on specific moderators including BDNF, apolipoprotein E and other genetic results, are not released to the patient, and this is specified in the consent form.

Study monitoring and inter-site coordination involve pertinent staff and study physicians at all sites with monthly to bimonthly teleconferences throughout the study. The coordinating site sends staff to other participating sites for study monitoring and quality control. The study PI (DPD) leads executive decision-making for study monitoring, quality control, dispute resolution, and regulatory issues.

Data Safety and Monitoring Board (DSMB)

Three independent experts with expertise in conducting clinical trials for agitation in AD form the DSMB. The DSMB reviews all SAEs and participates in an annual teleconference to determine if the study should continue, reviews study status SAEs and AEs, and then provides an actionable report to the Principal Investigator who forwards the DSMB report to the IRBs and NIA, which is the study sponsor.

Statistical Analysis, Sample Size, and Power Calculations

The primary analysis will be on the Intent-To-Treat (ITT) sample, including all randomized subjects according to the original treatment assignment. We estimate 15% dropout during the trial and will account for dropouts by examining the primary outcome variables using (longitudinal) linear mixed effects models (MEM)^{31, 32} for continuous outcomes or generalized mixed effects models for categorical outcomes. All tests for main effects will be performed at two-tailed significance $\alpha=0.05$, all tests for interaction effects will be performed at two-tailed significance $\alpha=0.15$ for this pilot study.

To test the primary hypothesis, i.e., lithium will significantly reduce agitation/aggression as compared to placebo, a linear mixed effects model will be used. For the secondary hypothesis, i.e., lithium will have greater proportion of responders compared to placebo, a chi-square test will be used. For the exploratory hypothesis, i.e., lithium will significantly reduce psychosis as compared to placebo, a linear mixed effects model will be used. For both the primary hypothesis and this hypothesis, we will first test the interaction effect of group and time.

To evaluate the tolerability of low dose lithium by assessing emergent side effects over the course of the 12-week trial on lithium compared to placebo, we will test whether the change in TESS score from baseline to week 12 differs significantly in the lithium and placebo

groups using a t-test. For the biomarkers, the relationship between change in BDNF serum levels (baseline to week 12) and changes in agitation/aggression score and psychosis score will be tested using correlation analyses. For rs11869731 SNP in the ACCN1 gene & 7q11.2 gene locus, we will examine the association between the presence of 1 or 2 G alleles at the rs11869731 SNP in the ACCN1 gene and changes in agitation/aggression and psychosis scores by ANOVA, and lithium response by a chi-square test between presence of the G allele and response vs. non-response. In exploratory analyses we will test for gene by treatment interaction to examine this SNP, and the number of VNTRs at the 7q11.2 gene locus (D7S1816), as potential treatment modifiers.

Power Analysis—We used the RMASS program for power analysis for longitudinal studies.³³ For a sample size of 80 patients, under moderate or weak correlations and a reasonable estimate of dropout, we have 80% power to detect a medium to large effect size, e.g., if dropout is 15% and correlation is 0.36 the effect size is 0.5.

Decision to move to a larger Phase III trial—In Lit-AD, if the effect size is medium or greater than medium, we will plan on conducting a larger trial as long as lithium does not show unacceptably poor tolerability (marked increase in AEs or SAEs compared to placebo). If the effect size is small to medium, we will consider a larger trial only if lithium is very well tolerated with little difference in SAEs and AEs compared to placebo. If the effect size is less than small, we will consider the results to provide insufficient evidence to proceed to a larger trial. The reason for this conservative approach to decision-making is that there are legitimate concerns about prescribing lithium in older adults with dementia because of its potential toxicity. Therefore, we will proceed with a larger trial only if the results of this trial show both evidence of efficacy and an acceptable safety profile.

Discussion

This is the first randomized, double-blind, placebo-controlled trial to assess the efficacy of lithium treatment for symptoms of agitation, with or without psychosis, in elderly adults who have Alzheimer's disease. Several design features were incorporated to provide unique strengths to this trial. Patients with comorbid Alzheimer's disease and neuropsychiatric symptoms of agitation/aggression with or without psychosis are identified and recruited from psychiatric, neurological, medical and other settings, thereby providing greater generalizability to the findings than in previous trials. The presence of an unblinded physician to generate sham lithium levels used by study physicians to determine dose adjustments allows us to follow and treat research subjects in both treatment arms in an identical manner and provides a template for future placebo-controlled trials of lithium treatment in these patients by maintaining the blindness of study physician raters and the integrity of the research. This study also evaluates, for the first time, the clinical applicability of well-defined genetic (apolipoprotein E, a SNP in intron 1 of the ACCN1 gene, and variation at the 7q11.2 gene locus) and neurobiological (BDNF) markers as moderators of neuropsychiatric improvement in patients with Alzheimer's disease.

Alternative study designs included open treatment with lithium followed by a blinded comparison of continuation lithium versus discontinuation to placebo, which is a design

used successfully to study antipsychotic discontinuation in a similar patient sample.²⁴ We chose a parallel group design because it is better suited to address side effects, which is a concern with lithium, and because the efficacy of lithium needs to be established first in a parallel group design before proceeding to a discontinuation trial. Another potential research strategy is to evaluate the utility of lithium as an add-on treatment to other specific psychotropic medication treatment, e.g., antipsychotics or antidepressants like citalopram.³⁴ This approach is worth considering as a follow-up strategy if efficacy with acceptable tolerability is observed in Lit-AD.

If lithium demonstrates efficacy in this pilot trial, we plan to proceed to a Phase III study based on the conditional strategy that has been outlined. The overarching goal is to obtain relevant information about three potential roles (these roles are not mutually exclusive) for low- dose lithium treatment if it is found to be effective and safe in Lit-AD: (1) first-line treatment; (2) adjunct treatment to antipsychotics in partial responders; (3) second-line agent after non- response or intolerability to antipsychotics or other psychotropic medications. Given the lack of demonstrated efficacy for anticonvulsants as mood stabilizers in these patients,^{14, 35} and the toxicity of antipsychotics limiting their use, the results of the Lit-AD trial are likely to have considerable impact in the field. Finding an effective, safe treatment for agitation/aggression is also important in other dementias, e.g., frontotemporal dementia (FTD), which is a common type of primary dementia. In FTD, behavioral changes, which are often very disruptive, are common and there is no proven effective treatment for these symptoms. We are beginning to address this gap in the field with a pilot lithium trial, using a similar design, to treat neuropsychiatric symptoms in FTD.

Acknowledgments

Funding

The study is supported by grant R01AG047146-01 from the National Institute on Aging, NIH, Bethesda, MD, USA.

Competing Interests

D.P. Devanand: Grant Support previous three years: National Institute on Aging, Avanir. Advisory Board: Acadia, Axovant, Eisai, Genentech.

Elizabeth Crocco: Grant Support previous three years: National Institute on Aging, State of Florida Department of Elder Affairs, Health Services Research Administration (HRSA), Otsuka, Novartis, Avanir, Neurim.

Speaker Honoraria: Excel continuing education, Pri-Med/CME, Baptist Health System, Miami FL.

Brent P. Forester: Grant Support previous three years: National Institute on Aging, Rogers Family Foundation, Assurex, Biogen, Eli Lilly, Roche

Advisory Board: Eli Lilly

Mustafa M. Husain: Grant Support previous three years: National Institutes of Health, National Institute of Mental Health, National Institute on Drug Abuse, National Institute of Neurological Disorders and Stroke, National Institute on Aging, Cyberonics, Brainsway, NeoSync, Alkermes, Assurex, Avanir.

Research Consultant: AtheaDx, Acadia.

Gregory H. Pelton: Grant Support previous three years: National Institute on Aging

References

1. Devanand DP, Jacobs DM, Tang M-X, et al. The course of psychopathologic symptoms in mild to moderate Alzheimer's disease. *Arch Gen Psychiatry*. 1997; 54:257–263. [PubMed: 9075466]
2. Lyketsos CG, Steinberg M, Tschanz, et al. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am J Psychiatry*. 2000; 157:708–714. [PubMed: 10784462]
3. Scarmeas N, Brandt J, Albert M, et al. Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol*. 2005; 62:1601–1608. [PubMed: 16216946]
4. Brodaty H, Arasaratnam C. Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. *Am J Psychiatry*. 2012; 169(9):946–53. Erratum in: *Am J Psychiatry* 2013;170(2):227. [PubMed: 22952073]
5. Ballard CG, Gauthier S, Cummings JL, et al. Management of agitation and aggression associated with Alzheimer disease. *Nature reviews: Neurology*. 2012; 5:245–55. DOI: 10.1038/nrneurol.2009.39
6. Hampel H, Ewers M, Bürger K, et al. Lithium trial in Alzheimer's disease: a randomized, single-blind, placebo controlled, multicenter 10-week study. *J Clin Psychiatry*. 2009; 70:922–931. [PubMed: 19573486]
7. Forlenza OV, Diniz BS, Radanovic M, et al. Disease modifying properties of long term lithium treatment for amnesic mild cognitive impairment: randomized controlled trial. *Br J Psychiatry*. 2011; 198:351–356. [PubMed: 21525519]
8. Macdonald A, Briggs K, Poppe M, et al. A feasibility and tolerability study of lithium in Alzheimer's disease. *Int J Geriatr Psychiatry*. 2008; 23:704–11. [PubMed: 18181229]
9. Havens WW 2nd, Cole J. Successful treatment of dementia with lithium. *J Clin Psychopharmacol*. 1982; 2:71–72. [PubMed: 7068945]
10. Holton A, George K. The use of lithium in severely demented patients with behavioural disturbance. *Br J Psychiatry*. 1985; 146:99–100. [PubMed: 3978352]
11. Randels PM, Marco LA, Hanspal NS, Robinson B. Possible lithium-induced extrapyramidal effects in Alzheimer's disease. *Hillside J Clin Psychiatry*. 1984; 6(1):117–121. [PubMed: 6571454]
12. Licht RW. Lithium: Still a major option in the management of bipolar disorder. *CNS Neuroscience & Therapeutics*. 2012; 18:219–226. DOI: 10.1111/j.1755-5949.2011.00260.x [PubMed: 22070642]
13. Schou M. Lithium treatment at 52. *J Affect Disord*. 2001; 67:21–32. [PubMed: 11869750]
14. Yeh YC, Ouyang WC. Mood stabilizers for the treatment of behavioral and psychological symptoms of dementia: an update review. *Kaohsiung J Med Sci*. 2012; 28(4):185–93. [PubMed: 22453066]
15. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine(US); 2000. Feb 29, Identifier NCT00703677, A Pilot trial of lithium in subjects with progressive supranuclear palsy or corticobasal degeneration; 2008 Jun 11[cited 2018 Mar 2]; [about 8 screens]. Available from: <https://clinicaltrials.gov/ct2/show/results/NCT00703677?sect=X43970156#othr>
16. Devanand DP, Pelton GH, D'Antonio K, et al. Low-dose Lithium treatment for agitation and psychosis in Alzheimer's disease and Frontotemporal dementia: A case series. *Alzheimer Disease & Associated Disorders*. 2017; 31:73–75. [PubMed: 27819842]
17. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34(7):939–44. [PubMed: 6610841]
18. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7(3): 263–9. [PubMed: 21514250]
19. Nichols TA, Drayton SJ, Borckardt J, et al. Lithium dosing equations: Are they accurate? *Annals of Pharmacotherapy*. 2014; 48(5):596–600. [PubMed: 24577145]

20. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA*. 2001; 285(10): 1299–307. [PubMed: 11255384]
21. Squassina A, Manchia M, Borg J, et al. Evidence for association of an *ACCN1* gene variant with response to lithium treatment in Sardinian patients with bipolar disorder. *Pharmacogenomics*. 2011; 12(11):1559–69. [PubMed: 21961650]
22. Turecki G, Grof P, Grof E, et al. Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. *Mol Psychiatry*. 2001; 6(5): 570–8. [PubMed: 11526471]
23. Leyhe T, Eschweiler GW, Stransky E, et al. Increase of BDNF serum concentration in lithium treated patients with early Alzheimer's disease. *J Alzheimers Dis*. 2009; 16(3):649–56. DOI: 10.3233/JAD-2009-1004 [PubMed: 19276559]
24. Devanand DP, Mintzer J, Schultz SK, et al. Relapse risk after discontinuation of risperidone in Alzheimer's disease. *N Engl J Med*. 2012; 367:1497–1507. [PubMed: 23075176]
25. Katz S, Akpom CA. A measure of primary sociobiological functions. *Int J Health Serv*. 1976; 6(3): 493–508. [PubMed: 133997]
26. Brorsson B, Asberg KH. Katz index of independence in ADL: Reliability and validity in short-term care. *Scand J Rehabil Med*. 1984; 16(3):125–32. [PubMed: 6494836]
27. McKnight RF, Adida M, Budge K, et al. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet*. 2012; 379(9817):721–8. [PubMed: 22265699]
28. Tredget J, Kirov A, Kirov G. Effects of chronic lithium treatment on renal function. *J Affect Disord*. 2010; 126(3):436–40. [PubMed: 20483164]
29. Janowsky DS, Buneviciute J, Hu Q, et al. Lithium-induced renal insufficiency: a longitudinal study of creatinine increases in intellectually disabled adults. *J Clin Psychopharmacol*. 2011; 31:769–73. [PubMed: 22020353]
30. Stevens LA, Viswanathan G, Weiner DE. CKD and ESRD in the elderly: Current prevalence, future projections, and clinical significance. *Advances in chronic kidney disease*. 2010; 17(4):293–301. DOI: 10.1053/j.ackd.2010.03.010 [PubMed: 20610356]
31. Brown H, Prescott R. *Applied Mixed Models in Medicine*. West Sussex, UK: Wiley; 1999.
32. Diggle PJ, Heagerty P, Liang KY, et al. *Analysis of Longitudinal Data*. 2nd. Oxford University Press; 2002.
33. Roy A, Bhaumik DK, Aryal S, et al. Sample size determination for hierarchical longitudinal designs with differential attrition rates. *Biometrics*. 2007; 63(3):699–707. [PubMed: 17825003]
34. Porsteinsson AP, Drye LT, Pollock BG, et al. Effect of Citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA*. 2014; 311(7):682–691. DOI: 10.1001/jama.2014.93 [PubMed: 24549548]
35. Tariot PN, Schneider LS, Cummings J, et al. Alzheimer's disease cooperative study group. Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. *Arch Gen Psychiatry*. 2011; 68(8):853–61. [PubMed: 21810649]

Table 1**Inclusion/Exclusion Criteria****Inclusion Criteria:**

- 1 Adult male or female.
- 2 Diagnosis of possible or probable Alzheimer's disease by standard NIA criteria (McKhann et al, 1984; McKhann et al, 2011)
- 3 Folstein MMSE 5-26 out of 30
- 4 Neuropsychiatric Inventory (NPI) agitation/aggression subscale score 4. On each subscale (frequency × severity), a score higher than 4 represents moderate to severe symptoms.
- 5 Female patients need to be post-menopausal
- 6 Availability of informant; patients without an informant will not be recruited. Patients who lack capacity must have a surrogate.

Exclusion Criteria:

- 1 Medical contraindication to lithium treatment or prior history of intolerance to lithium treatment. Contraindications to lithium in this study include: resting tremor causing functional impairment, history of falls in the last month, untreated thyroid disease or any abnormal thyroid function test (T3, T4, or TSH), serum creatinine level greater than 1.5 mg/100ml or a glomerular filtration rate less than 44ml/min/1.73m²
 Blood pressure > 150/90 mm Hg.
 Heart rate < 50 BPM.
 Unstable cardiac disease based on history, physical examination, and ECG.
- 2 Medications, in combination with lithium, known to have adverse renal effects, including therapeutic or high doses of diuretics, i.e. hydrochlorothiazide greater than 25 mg daily or furosemide greater than 10 mg daily.
 Whenever feasible, patients receiving concomitant antidepressants or antipsychotics will be washed off these medications for at least 24 hours before starting lithium. Patients who do not wish to discontinue antipsychotics or antidepressants, typically because of family member/caregiver objection, will be allowed to enter the trial provided there is no contraindication to concomitant lithium use with that specific psychotropic medication. During the trial, patients will be permitted to receive lorazepam as needed up to 1 mg per day for anxiety/insomnia, and non-benzodiazepine hypnotics, e.g., zolpidem.
- 3 Current clinical diagnosis of schizophrenia, schizoaffective disorder, other psychosis, or bipolar 1 disorder (DSM-IV TR criteria).
- 4 Current or recent (past 6 months) alcohol or substance dependence (DSM-IV TR criteria).
- 5 Current major depression or suicidality as assessed by the study psychiatrist.
- 6 Suicidal behavior or dangerous behavior with serious safety risk or risk of physical harm to self or others.
- 7 Parkinson's disease, Lewy body disease, multiple sclerosis, CNS infection Huntington's disease, amyotrophic lateral sclerosis, other major neurological disorder.
- 8 Clinical stroke with residual neurological deficits. MRI findings of cerebrovascular disease (small infarcts, lacunes, periventricular disease) in the absence of clinical stroke with residual neurological deficits will not lead to exclusion.
- 9 Acute, severe, unstable medical illness. For cancer, patients with active illness or metastases will be excluded, but past history of successfully treated cancer will not lead to exclusion.
- 10 QTc interval > 460 ms in the baseline EKG.
- 11 Hyponatremia as determined by serum sodium level > 150 meq/L.

Table 2

Flow Sheet and Procedures for Selected Major Time Points

Assessments	Screening	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Dosage Range (Lithium/Placebo)		150 mg	150- 300 mg	150- 450 mg	150- 600 mg	150- 600 mg	150- 600 mg	150- 600 mg
Informed Consent	X							
History and Clinical Evaluation	X							
Medication History		X						
Concomitant Medications		X						X
Lorazepam Dosage Form	X	X	X	X	X	X	X	X
Physical Examination	X							
Vital Signs	X	X	X	X	X	X	(X)	X
Inclusion/Exclusion Criteria	X							
Folstein Mini Mental State Exam (MMSE)	X							X
Severe Impairment Battery (SIB)		X						X
Clinical Dementia Rating (CDR)		X		X		X		X
CGI Behavior (CGI-S & CGI-C)		X	X	X	X	X	X	X
CGI Global (CGI-S & CGI-C)		X	X	X	X	X	X	X
Neuropsychiatric Inventory (NPI)	X	X	X	X	X	X	X	X
Young Mania rating Scale (YMRS)		X	X	X	X	X	X	X
Treatment Emergent Symptom Scale (TESS)		X	X	X	X	X	X	X
Get Up and Go		X						X
Simpson-Angus Scale (SAS)		X	X	X	X	X	(X)	X
Basic Activities of Daily Living (BADL)		X		X		X	X	X
Zarit Caregiver Burden Interview		X		X		X	X	X
Frequency of Contact Form	X	X	X	X	X	X	X	X
Cumulative Illness Rating Scaling (Geriatrics)		X						
Pill Dispense and Return Log			X	X	X	X	(X)	X
Protocol Exit Form								X
Randomization Form		X						
Serum Lithium Level			X	X	X	X	(X)	X

Assessments	Screening	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Lab Tests (includes RFTs, TFTs)	X				X			X
EKG	X							X
BDNF Levels		X						X
Blood for Genetic Studies		X						
Lithium Prescription		X	X	X	X	X	(X)	X
Review of Adverse Events		X	X	X	X	X	X	X

* (X) at week 10 denotes that procedure only be completed if in-clinic visit occurs rather than a phone interview that is permitted at this time-point.