Protocol Title: Treatment of Psychosis and Agitation in Alzheimer's disease

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Treatment of Psychosis and Agitation in Alzheimer's Disease

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Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am proposing an amendment only to an existing protocol

Division & Personnel

Division

What Area Group does the PI belong to?
What Division/Department does the PI belong to?
Division of Geriatric Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
n/a

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

None

Amendment

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Collection of Biological Specimens
✓ Studies of DNA
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ Off-label Use of Drug or Device

Population

Indicate which of the following populations will be included in this research

✓ Adults who may have impaired decision-making ability
✓ Adults who lack capacity to consent
✓ Adults
✓ Individuals with Psychosis

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
National Institute on Aging
Grant Name
Treatment of psychosis and agitation in Alzheimer's Disease
Grant Number
1R01AG047146-01
Select one of the following
Multicenter(NYSPI is the lead site)
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)

University of Miami Miller School of Medicine
McLean Hospital
University of Texas Southwestern Medical Center

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

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Symptoms of agitation/aggression with or without psychosis that commonly occur in patients with Alzheimer's disease (AD), are distressing to patients and caregivers, often lead to institutionalization, are associated with increased mortality, and are very difficult to treat. Worldwide, the prevalence of dementias, including AD, is rapidly increasing due to the aging population with a corresponding increase in the number of patients with dementia who develop symptoms of agitation/aggression with or without psychosis. Among the psychotropic medications studied in AD, only antipsychotics have been shown to be superior to placebo in randomized, double-blind, controlled trials.

Clinically, many patients with AD show no response or minimal response to antipsychotics for symptoms of agitation/aggression or psychosis, or they have intolerable side effects on these medications. Antipsychotics have a wide range of side effects, including the risk of increased mortality (60-70% higher rate of death on antipsychotic compared to placebo) that led to an FDA black box warning for patients with dementia; a more recent review and meta-analysis showed a 54% increased risk of mortality. Our published data on the persistence of agitation over prolonged periods in patients with AD, and the increased risk of relapse when antipsychotics are discontinued after maintenance of treatment response, indicate that antipsychotics may need to be prescribed for long periods in many patients with the attendant risks of longterm side effects and increased risk of mortality. In addition, some patients show only partial response to antipsychotics and symptoms persist. For these reasons, we need to study alternative treatment strategies. Currently, there is no FDA-approved medication for the treatment of psychosis or agitation in AD.

Our initial open treatment pilot data show that patients with no response or partial response to antipsychotics clearly improve on lithium, supporting the systematic study of lithium treatment for agitation/aggression with or without psychosis in AD. Our innovative project will examine the efficacy and side effects of low dose lithium treatment of agitation/aggression with or without psychosis in 80 patients with AD in a randomized, doubleblind, 12-week trial (essentially a Phase II trial). The results will determine the potential for a large-scale clinical trial (Phase III) to establish the utility of lithium in these patients.

Background, Significance and Rationale

Background, Significance and Rationale
Symptoms of psychosis or agitation are common in Alzheimer's disease. These symptoms are associated with distress for the patient, an increased burden for caregivers, more rapid cognitive decline, greater risk of institutionalization and mortality, and increased health care costs. In a recent meta-analysis, caregiver education and behavior modification studies revealed a small to medium effect size in treating agitation in these patients. However, none of these studies were double-blind (difficult to achieve in such studies) and none had a control group that received the same amount of staff time as the intervention group, thereby biasing the results toward the active intervention. The value of behavioral strategies typically is limited in patients with severe agitation and psychosis. Large, well-controlled trials with an adequate control group remain to be conducted to establish the utility of caregiver education and behavioral intervention strategies.

Among the psychotropic medications that have been studied, only antipsychotics have shown superiority over placebo for the treatment of psychosis and agitation in patients with dementia.
However, most studies show only moderate superiority for antipsychotic over placebo and a few studies have been negative. The side effects of antipsychotic medications include sedation, extrapyramidal signs, tardive dyskinesia, weight gain, and the metabolic syndrome. A pooled analysis from 17 short-term trials showed that the mortality rate in patients with dementia receiving antipsychotic medications was 1.6 to 1.7 times as high (60-70% increase in mortality rate) as the mortality rate in patients receiving placebo. These findings led the FDA to issue a black-box warning for antipsychotic medication use in patients with dementia; a more recent meta-analysis reported a slightly lower odds ratio of 1.54 (54% increase in mortality rate).

In an NIA-funded, multicenter, randomized, double-blind trial in 180 patients with AD and symptoms of psychosis or agitation/aggression, we showed that after response to open treatment with the atypical antipsychotic risperidone (16 weeks), randomized discontinuation to placebo was associated with a significantly increased risk of relapse 16 weeks later and 32 weeks later compared to continuation risperidone. Although the increased likelihood of relapse after discontinuation is a concern, Federal regulations in nursing homes continue to require discontinuation of antipsychotics 3-6 months after initiating treatment unless the treating physician provides written justification to continue the antipsychotic. Further, the risk of adverse effects has led the Center for Medicare and Medicaid Services (CMS) to require a 15% reduction of antipsychotic use in patients with dementia in nursing homes. Clearly, while antipsychotics may play an important therapeutic role, their adverse effects impede their use and new medication approaches need to be investigated.

The selective serotonin reuptake inhibitor (SSRI) citalopram and risperidone showed similar response rates in one trial, and a placebo-controlled trial of citalopram (CitAD) is now being conducted for AD patients with agitation. The utility of SSRIs in these patients, however, remains to be established. One criticism of antipsychotics in the treatment of agitation in dementia is that they are sedating and that this is erroneously observed as improvement in agitation. However, in the CATIE-AD trial the highly sedating antipsychotic, quetiapine, was found to be less effective than risperidone, which is not as sedating.

Further, there has been little correlation between sedation and improvement in agitation in antipsychotic treatment studies. Sedation is not a common side effect of lithium and should not be an issue in our proposed trial. Anticonvulsants are widely used to treat agitation in AD. Early small-scale studies suggested efficacy for carbamazepine to treat psychosis and agitation in AD, but there were negative studies. However, carbamazepine is a relatively toxic anticonvulsant that can lead to liver damage and blood dyscrasias. Large-scale studies with the widely used anticonvulsant medication valproate failed to show superiority over placebo in treating agitation and psychosis, and valproate did not prevent the emergence of agitation or psychosis in patients with dementia. Other anticonvulsants, including lamotrigine and gabapentin, have not been studied in placebo-controlled trials in these patients. Manic-like symptoms are uncommon and full-blown mania is very rare in AD. Lithium has several different actions from anticonvulsants, though both are effective in bipolar disorder, especially mania. Lithium is not being proposed here to treat mania in AD though we will monitor symptoms on the Young Mania Rating Scale.

In patients with AD, lithium has been studied for its putative cognitive enhancing effects. A few reports suggest that chronic lithium use reduces the risk of dementia, but other data show increased dementia risk

with lithium use. A placebo-controlled, single-blind lithium trial showed no cognitive effects in patients with AD, but a recent trial of lithium in 45 patients with mild cognitive impairment (MCI, which often leads to clinically diagnosable AD) showed a small advantage for lithium (n=24) over placebo (n=21) in attention and other cognitive domains. None of these studies with lithium were intended to treat psychosis or agitation in AD, and patients with these symptoms typically were excluded in these clinical trials. There has been no systematic placebo-controlled trial of lithium to treat agitation/aggression with or without psychosis in AD even though lithium is a highly effective treatment for mania with psychosis and symptoms of agitation or aggression. Nonetheless, the published studies of lithium to treat cognitive decline in older patients provide valuable data about the safety of low-dose lithium in patients with MCI or AD.

Specific Aims and Hypotheses

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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.

Primary Hypothesis. Over these 12 weeks, the agitation/aggression domain score on the Neuropsychiatric Inventory (NPI) will decrease significantly more on lithium than placebo.

Secondary Hypothesis. Over these 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) plus a CGIChange score of much improved or very much improved (CGI based on these 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 (baseline, 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. We do not postulate a specific mechanism of action for lithium in our trial, but will evaluate these three potential predictors of lithium response with the aim of improving patient selection for personalized treatment. We will examine BDNF serum levels as a biomarker correlate of lithium treatment by correlating change in BDNF levels with change in NPI agitation/aggression and psychosis scores.

Description of Subject Population

Sample #1

Specify subject population
Adults with possible or probable Alzheimer's disease (AD)
Number of completers required to accomplish study aims
68
Projected number of subjects who will be enrolled to obtain required number of completers
80
Age range of subject population
18 and older

Gender, Racial and Ethnic Breakdown
Eighty outpatients will be recruited through the Columbia University Alzheimer's Disease Research Center (ADRC; Memory Disorders Clinic and Behavioral Neurology Practice Group) over 4.2 years (19 patients per year). Based on our previous studies recruiting a similar subject population, the estimated gender distribution is 55% female with an ethnic distribution of 65% non-Hispanic White, 20% Hispanic, 12% African American, and 3% Asian American.
Description of subject population
Adults, male or female, with a diagnosis of possible or probable AD by NINCDS- ADRDA and possible or probable AD dementia by the new NIA criteria.

Recruitment Procedures

Describe settings where recruitment will occur
The Memory Disorders Center (MDC) at the New York State Psychiatric Institute (NYSPI) and the Behavioral Neurology practice group at the Neurological Institute (New York Presbyterian Hospital) are our main sources of recruitment for studies of patients with AD. Drs. Devanand, Pelton and Huey are attending psychiatrists in these settings. In this protocol, we will treat only outpatients. Other sources of recruitment include advertising on electronic media such as online forums for caregivers of AD patients, web postings through the site studykik.com and recruit.cumc.columbia.edu, as well as posting the approved study fliers at medical centers and caregiver support groups for AD patients.

How and by whom will subjects be approached and/or recruited?
All patients will be recruited by Drs. Devanand, Pelton and Huey. We will also submit the attached flyer to local media, web postings through the site studykik.com and recruit.cumc.columbia.edu, as well as post it in medical centers and at caregiver support groups to advertise specifically for the study.

Timeline for recruitment.

Day 1: screening for inclusion/exclusion criteria. If eligible the patient and informant will be approached by one of the study physicians to obtain informed consent. Informed consent will be completed on the screening day or at the baseline visit in patients/informants who may need to think over the study before

signing informed consent.

Week 1: complete baseline visit and start study medication or placebo for the 12-week trial. In patients where there is clinical urgency, the screening and baseline visits may be merged into a single visit and all procedures will be completed on the screening day itself. Procedures will be conducted according to the schedule described in the table under "Procedures."

How will the study be advertised/publicized?
The proposed study will be conducted at the New York State Psychiatric Institute with patients recruited by Drs. Devanand, Pelton, and Huey. Additionally, the attached flyer will be submitted to local media, web postings through the site studykik.com and recruit.cumc.columbia.edu, as well as post it in medical centers and at caregiver support groups to advertise specifically for the study.

Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
02129348

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
No

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Patients with possible or probable AD
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion Criteria	Method of Ascertainment
1. Diagnosis of possible or probable AD by standard NIA criteria (McKahnn et al, 1984; McKhann et all, 2011).	Physician evaluation
2. Folstein MMSE 5-26 out of 30.	Neuropsychological evaluation
3. Neuropsychiatric Inventory (NPI)	Physician evaluation

agitation/aggression subscale score ≥ 4. On each subscale (frequency X severity), a score higher than 4 represents moderate to severe symptoms.	
4. Female patients need to be post-menopausal	Patient and informant interview
5. Availability of informant; patients without an informant will not be recruited. Patients who lack capacity must have a surrogate.	Physician Evaluation

Create or insert table to describe the exclusion criteria and methods to ascertain them

Exclusion Criteria	Method of Ascertainment
1. Medical contraindication to lithium treatment or prior history of intolerability 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), 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.	Evaluation
2. Medications, in combination with lithium, known to have adverse renal effects**,** including therapeutic or higher	Physician Evaluation

doses of diuretics, i.e. hydrochlorothiazide greater than 25mg daily or furosemide greater than 10mg 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/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).	Physician Evaluation
4. Current or recent (past 6 months) alcohol or substance dependence (DSM-IV TR criteria).	Physician Evaluation
5. Current major depression or suicidality as assessed by the study psychiatrist.	Physician Evaluation
6. Suicidal behavior or dangerous behavior with serious safety risk or risk of physical harm to self or others.	Physician Evaluation
7. Parkinson's disease, Lewy body disease, multiple sclerosis, CNS infection, Huntington's disease, amyotrophic lateral sclerosis, other major neurological disorder.	Physician Evaluation
8. Clinical stroke with residual	Physician Evaluation

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.	Physician Evaluation
10. QTc interval > 460 ms at the time of baseline EKG is an exclusion criterion for treatment.	EKG reading by physician.
11. Hypernatremia as determined by serum sodium level > 150 meq/L	Evaluation

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
Yes
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process

Verbal consent is obtained before continuing with phone screening.
Describe Study Consent Procedures
All patients at enrollment will be assessed for capacity and this will be documented in the chart. For patients who retain the capacity to consent, voluntary informed consent will be obtained from all subjects by Drs. Devanand, Pelton or Huey. Typically, patients with Folstein MMSE greater than 20 out of 30 retain the capacity to consent.

For patients who lack the capacity to consent, as is expected for the majority of patients in this study, the required NYSPI/Columbia IRB-approved surrogate consent procedures will be followed as detailed below. At baseline, patients who lack the capacity to consent will be required to have the capacity to appoint a surrogate and then the patient will need to appoint the surrogate. In patients who lack the capacity to consent, if the patient lacks the capacity to appoint a surrogate or does not wish to appoint a surrogate the patient will not be included in the study. Under no circumstance will a patient objecting to participation be included in the study.

The consent form describes the nature of the procedures and time requirements, potential risks, the confidentiality of information, and the rights of research subjects, including their right to withdraw from the research at any time without loss of benefits to which they are otherwise entitled. It is made explicit that this protocol involves a randomized controlled trial in which the patient will be randomly assigned to Lithium or placebo for a 12-week period. The consent process also includes documentation of permission to obtain previous medical records.

The informant also signs a separate consent form indicating willingness to provide information (rating scales) about the patient. The IRB-approved forms for informed consent and for assessment of capacity are made part of the patient's permanent medical record, with a copy being filed in the research chart. The IRB-approved forms for informed consent and for assessment of capacity are made part of the patient's permanent medical record, with a copy being filed in the research chart.

Clinical Settings and Consent Procedures.
Memory Disorders Clinic. Memory Disorders Clinic physicians include Drs. Devanand, Pelton, and Huey who work in a supervisory capacity. Evaluations are conducted by Neurology fellows. If a patient is potentially eligible, these fellows will briefly describe the study and if the patient is interested then refer the patient to Dr. Devanand or Dr. Pelton or Dr. Huey (whoever is available at that time). Therefore, in this setting patients will first be approached about the study by a non-study physician.

Behavioral Neurology Practice Group. Dr. Huey, but not Dr. Devanand or Dr. Pelton, is a member of this group. If the other Neurology faculty physician in this group believes that a patient is potentially eligible, this physician will briefly describe the study and if the patient/caregiver is interested then refer the patient to Dr. Devanand or Dr. Pelton or Dr. Huey (whoever is available at that time). If Dr. Huey evaluates a patient who may be eligible, he will explicitly inform them that they have the option of getting a second opinion regarding study participation from a physician in the clinical setting who is not an investigator in the study, and immediately arrange for that second opinion if requested.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following
We are requesting a waiver of consent for family history information gathered from secondary subjects.

Explain why your research can not be practicably carried out without the waiver or alteration
The federal regulation 45CFR46.116(d) states that an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that: (1) The research involves no more than minimal risk to the subjects; (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) The research could not practicably be carried out without the waiver or alteration; and (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Describe whether and how subjects will be provided with additional pertinent information after participation
These subjects will not be provided with additional information after participation.

Assent Procedures

Describe procedures by which subject assent will be assessed and/or recorded
The IRB-approved forms for informed consent and for assessment of capacity are made part of the patient's permanent medical record, with a copy being filed in the research chart.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Devanand, Davangere, MD

Huey, Edward, MD
Pelton, Gregory, MD
Type in the name(s) not found in the above list
Huey, Edward, MD

Independent Assessment of Capacity

You have indicated that your study involves subjects who MAY LACK capacity to consent.
Does this study require an independent assessment of capacity?
Yes
Methods/procedures for capacity assessment

As stated under Consent Procedures, for patients who lack the capacity to consent, as is expected for the majority of patients in this study, the required NYSPI/Columbia IRB-approved surrogate consent procedures will be followed. At baseline, patients who lack the capacity to consent will be required to have the capacity to appoint a surrogate and then the patient will need to appoint the surrogate. In patients who lack the capacity to consent, if the patient lacks the capacity to appoint a surrogate or does not wish to appoint a surrogate the patient will not be included in the study. Under no circumstance will a patient objecting to participation be included in the study.

You have indicated that your study involves subjects who DO LACK capacity to consent. Please justify

The nature of Alzheimer's disease is that some patients may not have the capacity to consent but it is important to include these patients if possible in the protocol to ensure representativeness of the sample and to avoid inclusion bias. Therefore, inclusion of these subjects is justified.

Procedures for surrogate consent

At NYSPI, OMH regulations require that in patients who lack the capacity to consent, surrogate consent is acceptable when all the following procedures are conducted:

1. A psychiatrist or licensed clinical psychologist who is independent of the research must confirm that the patient still retains the capacity to designate a surrogate, i.e., identify the surrogate and indicate that the surrogate can consent on the patient’s behalf for the research study. Drs. Bret Rutherford, Joel Sneed, Karen Marder, Karen Bell, Joan Prudic, Scott Small, Sarah Janicki, Clara Boyd, Alon Seifan, and Jamie Noble will be the independent evaluators for this study. They will follow the procedures described here using the forms attached as an addendum to the Informed Consent Form. 2. The document designating the research surrogate must be witnessed by two persons who are independent of the research. The psychiatrist or licensed clinical psychologist who assesses the patient’s capacity to choose a surrogate may also be witness to the choice of the surrogate.

3. If the patient chooses a surrogate but is unable to sign the document, another person may sign for the patient and the two witnesses shall, in writing, confirm the patient's choice of a surrogate and witness the signature of the person signing for the patient.

4. The surrogate cannot function as a witness to the choice of the surrogate. A family member or friend of the patient who is not the surrogate may function as a witness.

5. The surrogate cannot be an administrator or employee of the facility at which the research is conducted or the facility conducting the research. This restriction does not apply if the person is related to the patient by blood, marriage, or adoption. The selection of a patient's spouse as a surrogate is revoked upon the legal separation or divorce of the patient and spouse unless the patient specifies otherwise.

6. Notice of the appointment of a surrogate must be provided to the Mental Health Legal Service (MHLS). We will inform MHLS each time a patient who lacks capacity to consent and appoints a surrogate is recruited for this protocol.

Study Procedures

Describe the procedures required for this study
We will follow the procedures successfully used for blinded lithium levels in controlled trials in mood disorders. A physician independent of the study will receive lithium levels. This physician will provide the actual lithium level to the study physician for patients randomized to lithium, and make up a comparable "sham" level for patients on placebo. Dr. Devanand will be the Principal Investigator as well as a study physician. He will make executive decisions including study monitoring, regulatory issues, quality control (QC), and dispute resolution. He will have overall responsibility for the clinical care of the patients during the course of the study.

Dr. Pelton will be the Co-Investigator and the second study physician. He will evaluate the patients during the visits and be responsible for the clinical care of the patients during the course of the study.

Dr. Huey will be a Co-Investigator and a study physician. He will evaluate the patients during the visits and be responsible for the clinical care of the patients during the course of the study.

Research Assistant. This individual will be responsible for the conduct of all cognitive testing (at screening and during the study), other research procedures, data checking and integrity for all the data ensuing from this project.

Most patients participating in this study will not be able to provide detailed, accurate information during an interview because of their severity of dementia. The informant will provide this information about the patient, including relevant portions of the NACC clinical history (such as the Hachinski Ischemic Score & Cerebrovascular Disease form, Schwab and England and Activities of Daily Living Scale, and Subject Medications form) and the entire NPI, TESS, Young Mania Rating Scale, CGI, Clinical Dementia Rating and Basic Activities of Daily Living scales. The somatic side effect rating scale (TESS) will incorporate the

report of the patient as well. The efficacy rating scales (NPI, CGI, Young Mania Rating Scale) will incorporate behavioral observation of the patient and patient's report of symptoms. The Get Up & Go scale will be performed to assess patient's gait, balance, and fall risk.

These evaluation strategies are the current standard in clinical trials of treatment of agitation-aggression with or without psychosis in patients with dementia.

SCREENING VISIT

As part of the evaluation, a history is obtained to include age, age-at-onset of memory problems, handedness, education, occupation, medical and psychiatric history. Concurrent medications will be documented at all visits. Blood work will be done (SMAC, CBC, thyroid functions T3, T4, TSH, and renal functions including creatinine and urea as part of the SMAC). Blood pressure and heart rate will also be recorded at this visit as well as weight and height.

Patients who are found to be eligible at the screening visit will be randomized to treatment with lithium or placebo. Patient randomization will be stratified according to their classification, determined at the screening visit, as either psychotic or not psychotic. To classify patients as psychotic or not psychotic the following criterion will be used:
a. Patients receiving Neuropsychiatric Inventory (NPI) hallucination or delusions subscale scores ≥ 4 will be classified as psychotic. On each subscale (frequency X severity), a score higher than 4 represents moderate to severe symptoms.

STUDY VISITS

Patients who are enrolled will be asked to come for the baseline visit, typically 1 week after the screening visit. Subsequent study visits are at weeks 2, 4, 6, 8, 10, 12. Weekly visits are often not practically feasible for the caregiver (usually a family member) in patients with AD who are agitated or psychotic because the caregiver needs to bring, or arrange to bring, the difficult-to-manage patient to the appointment. Therefore, the visits are at 2-week intervals. However, if clinically indicated, the patient will be brought in for additional weekly visits at the intervening time-points. The week 10 visit is optional and ratings will be conducted by phone at week 10 if the patient is clinically stable at week 8 and a week 10 visit is not considered to be clinically necessary.

Washout Procedures. 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/day for anxiety/insomnia, and non-benzodiazepine hypnotics, e.g., zolpidem. No patient who is currently responding to a concomitant medication will be washed off of it.

Psychotropic medications will be washed out from 0 days to 14 days based on the specific psychotropic being used (14 days for fluoxetine or patients receiving high doses of antidepressants or other psychotropics, 7 days or fewer for other situations). The lithium/placebo protocol will begin the day after the last day of psychotropic is received during washout. We recognize that this is shorter than used in most psychotropic

medication trials in psychiatry, but is necessitated by the nature of the patients being studied that will require prompt study entry to ensure recruitment. There is no reason to suspect significant adverse interaction between any psychotropic medication and lithium carbonate 150 mg daily which is the dose that will be used in the first 2 weeks after randomization. Of note, this short washout strategy was used in our ADAD trial (Devanand et al NEJM 2012) and the CitAD trial (Porteinsson et al, JAMA 2014) for which we were a site and Devanand and Pelton were co-authors. The dropout rate in both these studies was lower than that in any other published large-scale trial of psychotropic medications to treat agitation with or without psychosis in patients with dementia. We believe that this psychotropic medication washout strategy contributed to our success.

Of note, patients do not need to be washed off psychotropic medications to participate in our proposed trial, and we expect half the sample to continue to receive other psychotropics including antipsychotic medications during the trial. Essentially, washout will be conducted only when it is deemed to be safe and acceptable to do so by the study physician in consultation with the patient and caregivers.

Lithium oral dose. Drs. Devanand, Pelton or Huey will prescribe generic lithium carbonate/placebo. The patient will be started on lithium/placebo 150mg/day, with subsequent dose titration to 300mg/day at the 2-week visit, 450mg/day at the 4-week visit, and 600mg/day (maximum daily dose) if tolerated and based on real/sham lithium blood level. This upward dose titration will occur only if clinically indicated (absence of response at lower doses without intolerable side effects). Patients who develop side effects, e.g., tremor, falls, will have their dose reduced.

Lithium levels will be drawn approximately 12-14 hours after the last dose, typically in the morning for patients who took their last dose of lithium/placebo the previous night.

Dosing change will involve instruction to the patient/caregiver over the telephone after the serum lithium level result is obtained from the week 2 blood draw and before the week 4 visit. At week 4 (patient on lithium/placebo 150mg/day or 300mg/day since week 2), blood to obtain the serum lithium level will again be drawn and the oral dose adjusted up to 450-600mg/day over the telephone after the serum lithium level result is obtained and before the week 6 visit based on the serum level obtained and clinical response and side effects. At week 6, the serum lithium level (patient on an oral dose of 150mg to 600mg/day, the maximum daily dose) will be drawn with subsequent dose adjustment based on procedures similar to those employed at week 2 and week 4. We will also draw a lithium level at week 8 with subsequent dose adjustment if indicated. We expect the dose to remain stable from week 8 to week 12 for essentially all patients, and the week 10 visit will be optional with telephone ratings conducted for patients who cannot come in to the clinic at that time-point. Patients who are clinically unstable will be required to come for the week 10 visit. Serum lithium level will be repeated at week 12. During the trial, patients will be permitted to receive lorazepam as needed up to **1** mg/day for anxiety/insomnia.

We are targeting a lithium level of 0.2 to 0.6 mmol/l. This low, fairly wide blood level range is chosen because of the potential increased toxicity risk in the elderly, even though the studies reviewed earlier do not show significant toxicity at low oral doses and blood levels in patients with dementia. Lithium levels will be assayed in the laboratory at the Nathan Kline Institute in Rockland. Clinical response of symptoms and side effects experienced by the patient will be primary in guiding oral lithium dose adjustment, and will override the information obtained from serum lithium levels if such a choice needs to be made.

Blinded lithium levels. Serum lithium levels will be assayed using standard, reliable clinical assay procedures at New York Presbyterian Hospital. This laboratory routinely conducts serum lithium level assays in patients with bipolar disorder and maintains high reliability. We will follow the procedures successfully used for blinded lithium levels in controlled trials in mood disorders. A physician independent of the study will receive lithium levels. This physician will provide the actual lithium level to the study physician for patients randomized to lithium, and make up a comparable "sham" level for patients on placebo.

At each follow-up visit, blood draws will take place approximately 12-14 hours after the previous night's lithium or placebo dose. In order to ensure that study physicians, research staff, and patients are unaware of medication assignment, the physician independent of the study will receive all the lithium levels. This physician will provide the actual lithium level to the study physician for patients actually taking lithium, and will make up a comparable "sham" lithium level for patient taking placebo. "Sham" lithium levels are defined as imitation lithium levels which are not reflective of the patient's actual blood lithium level and are only relevant to those patients taking placebo. This "sham" level will vary from low to high levels and will be largely based on the number of pills taken by the patient. Based on the blood level received and clinical response and tolerability, the study physician will adjust the number of pills at study visits. Lithium levels will be an important factor taken into account, but clinical response and side effects will be central in decision-making.

Blindness of raters. Raters will remain blind to randomized treatment condition (lithium or placebo) and will receive real or sham lithium blood levels based on the operational parameters described above.

Lithium dosing strategy. Lithium and placebo will be prescribed in identical-looking capsules made up by the NYSPI pharmacy.

Blood for SMAC (including creatinine), CBC, thyroid functions (T3, T4, TSH) will be drawn at baseline, week 6, and at 12 weeks. Creatinine and eGFR levels will be closely monitored and compared to baseline. If the eGFR declines to less than 44 ml/min or the serum creatinine level increases to more than 1.5 times the baseline level or if there is a > 0.3 mg/dl (>26.5mmol/l) increase in serum creatinine, treatment with lithium or placebo will be stopped. For patients who have improved on lithium, the laboratory values at 12 weeks will help to make the decision as to whether lithium can be safely continued, which will occur if TFTs and creatinine remain within range (TFTs within normal limits, creatinine and eGFR criteria as specified above).

Response will be defined as a 30% decrease in NPI core score (sum of subscales for delusions, hallucinations and agitation/aggression) and a CGI change score of much improved or very much improved (CGI based on psychosis/agitation, not on severity of dementia) from baseline to 12 weeks.

If treatment with lithium/placebo needs to be interrupted due to medical illness or surgery or any other reason at any time point in the study, interruption for up to 30 days will be permitted in this study. Research treatment with lithium/placebo will then resume and clinic visits will continue as scheduled.

Safety Monitoring during the course of the entire study will include vital signs assessment, physical exams, laboratory tests, monitoring of adverse events (TESS, and open-ended interview), and monitoring of concurrent medication records. As needed, communication with the patient's primary physician will also take place. A DSMB will be appointed in consultation with NIA.

All adverse events occurring after signing the consent forms, regardless of adherence to study treatment, will be recorded at all contacts with the patient. At scheduled visits, patients/informants will be interviewed about whether the patient experienced any symptoms or side effects since the last visit. Adverse events will be recorded and an adverse event form will be completed. If adverse events are noted, they will be rated as mild, moderate, or severe based on their clinical severity and frequency. The PI will inform the IRB immediately after knowledge of death, or of an event that is life-threatening that results in hospitalization, or that involves persistent or significant disability or incapacity (these will be rated as Serious Adverse Events). Data collected regarding these serious adverse events will include the treatment provided, outcome, and presumed relationship to study drug and will be updated as new information becomes available.

Medication Adherence will be assessed by pill counts done by the research assistant under the supervision of the study physician. Patients who return more than 25% of the pills that should have been taken will be rated as non-adherent for that visit. Non-adherence by itself will not lead to study termination, but the presence of non-adherence will be taken into account in the statistical analyses.

Implications. Patients with AD who develop agitation with or without psychosis are difficult to treat, and the development of these types of symptoms is the most common precipitant for institutionalization. In the absence of established effective, safe treatments for these symptoms, if lithium proves to be safe and effective and superior to placebo, this will provide important initial pilot data for the investigators to subsequently apply for funding to conduct a randomized, double-blind, placebo-controlled trial.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation
Dropout. Patients who cannot tolerate lithium will be offered treatment with alternative medications, e.g., an antipsychotic medication that they did not receive earlier. Creatinine and eGFR levels will be closely monitored as part of the SMAC done at baseline, week 6 and week 12. At 6 weeks, if the eGFR declines to less than 44 ml/min or the serum creatinine level increases to more than 1.5 times the baseline level or if there is a > 0.3 mg/dl (>26.5mmol/l) increase in serum creatinine, treatment with lithium or placebo will be stopped and alternative treatment strategies will be employed. The same criteria will apply to the 12-week time-point, and patients on lithium or placebo who do not meet the above kidney function test requirements will not receive lithium post-study. For patients who terminate treatment before 12 weeks, the study physician will terminate the protocol and an early termination visit will be completed. The blind will be broken by a physician independent of the research for all patients who exit randomized treatment, i.e., either early due to dropout from randomized treatment or after completion of the protocol. Therefore, the physician will be able to treat the patient in an informed manner. Patients who discontinue placebo will be offered open lithium treatment as the first option but all other clinically appropriate psychotropic medication strategies will also be considered.

If during the course of the trial, a patient demonstrates suicidal behavior or dangerous behavior with serious safety risk or risk of physical harm to self or others, the patient will be withdrawn from the protocol and receive open treatment.

For patients who do not make an appointment, every effort will be made to maintain the patient in the study including making a home visit if feasible. Patients who develop intolerable side effects even at the lowest permitted dose will be terminated from the protocol by the study investigator. The study investigator can also terminate the protocol if severe medical illness warrants study termination. The decision to terminate the protocol will be determined primarily by the presence of side effects that will take precedence over lithium levels.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
Routine Laboratory Tests: At baseline, week 6, and at 12 weeks, blood will be collected for the following screening laboratory tests that will be performed by the OMH Clinical Laboratories-Nathan Kline Institute: CBC, BUN, creatinine, eGFR, electrolytes, liver and thyroid function studies (total of 20 ml).
In addition, blood for lithium level (10 ml, also sent to NKI) will be obtained at week 2, week 4, week 6, week 8 (with subsequent dose adjustment if indicated), and week 12 in the protocol.

Genetic studies: Apolipoprotein E genotype is the best replicated genetic association with late-onset AD and its effect appears to be stronger than all the other genes shown to be associated with late onset AD. We do not postulate a hypothesis for apolipoprotein E genotype, but will examine it in exploratory analyses because of its strong association with AD. For all genetic assays, blood will be collected at baseline (8.5 ml) and DNA extracted in the Human Genetics Research Core laboratory at Columbia University. DNA will be analyzed in Dr. Lorraine Clark's laboratory at Columbia University for apolipoprotein E genotype, ACCN1 gene (SNP located in intron 1) and 7q.11.2 gene locus.

Throughout the 12-week trial the total amount of blood taken is 68.5 ml.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

Assessment	Time Allotment
NACC Clinical Evaluation by Physician	20 min
Treatment Emergent Symptom Scale (TESS)	4 min
GCI (behavior and global)	5 min

Clinical Dementia Rating (CDR)	2 min
Cumulative Illness Rating Scale (Geriatric)	5 min
Other Scales/Assessment	Time Allotment
Basic ADL Scale	5 min
NPI Neuropsychiatric Inventory	20 min
Get Up & Go	2 min
Zarit Caregiver Burden Interview	10 min
Simpson-Angus Scale	10 min
Young Mania Rating Scale (YMRS)	2 min
Neuropsychological Testing	Time Allotment
Folstein Mini Mental State Exam (MMSE)	5 min
Severe Impairment Battery (SIB)	20 min

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
1

Drug #1

Name of the drug
Lithium
Manufacturer and other information
We will use the generic version of lithium carbonate supplied to the NYSPI pharmacy.
Approval Status
No IND is required
Choose one of the following options
FDA conditions are met (see 'Rules')
Explain
Under Section 505 (i) of the Federal Food, Drug and Cosmetic Act (FDCA), we believe that this study meets all the requirements for exemption from the IND regulations (we have no intention to apply for a patent, and the other criteria in Section 505 (i) are also met).

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment

The maximum duration of delay to treatment is 12 weeks, during which the patient may be treated with Lithium or placebo.
Maximum duration of delay to standard care or treatment of known efficacy
The delay to treatment is up to 12 weeks. However, no specific treatment for agitation/aggression with or without psychosis has been FDA-approved in patients with dementia. Also, patients starting on concomitant psychotropics that cannot be washed out will be permitted to stay on them during the trial, and lorazepam is available as a rescue medication.
Treatment to be provided at the end of the study
After the study ends, the patient will continue to be followed in our ADRC by the physician who was following the patient prior to the start of the study, and will continue lithium or use alternative medications as clinically indicated.

Clinical Treatment Alternatives

Clinical treatment alternatives
Alternative medications include antipsychotics, and these are presented and discussed in the consent form.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Possible side effects of lithium include diarrhea, vomiting, shakiness, drowsiness, slowed thinking, weakening of muscles, difficulty concentrating, acne, weight gain, change in thyroid function (a hormone that regulates metabolic and other functions), increased urination (more frequent and more volume), bradycardia and hypernatremia. Hypernatremia is a condition caused by high levels of sodium in the blood that can occur due to dehydration, often due to lack of intake of fluids. Symptoms include dry mouth, weakness, lethargy, increased confusion, irritability and heart palpitations, and seizures can occur. If you experience any of these symptoms, report them to your study doctor immediately. Because of the possibility of becoming sleepy, patients will be instructed to be cautious about driving especially when the medication is started or the dose is raised. Renal functions will be monitored as noted earlier.
Describe procedures for minimizing risks

There are three areas in which safeguards to protect subjects from undue risk require discussion. These include the procedures used to obtain informed consent, the procedures used to ensure confidentiality of subjects' responses and findings on tests, and the procedures used to minimize possible risks associated with the research procedures.

Informed Consent. Informed consent is obtained and documented with a signed consent statement giving full information about the study. In the consent form and in discussion with an investigator, subjects are advised fully of the procedures to be used, the amount of time required of them, the fact that this is a longitudinal treatment study with repeated assessment at specified time points, the possible risks and benefits of the procedures and the treatment conditions, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigator.

Capacity to Consent. Based on IRB requirements, patients will be recruited by a study physician who signs the consent form in addition to the patient and informant. As described earlier, for patients who lack the capacity to consent but retain the capacity to appoint a surrogate, we will follow the procedures required by the NYSPI IRB (based on New York State OMH regulations) regarding assessment of capacity to consent.

Research Procedures. We have described above the potential risks of the research procedures and the safeguards that will be used to minimize risks. These include termination of subjects from research participation if it is believed that such participation endangers their welfare. Monitoring procedures are used to evaluate potential side effects of research procedures. The protocol stipulates an extensive medical, neurological, and psychiatric evaluation of all subjects as a condition for research participation.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
Confidentiality of Subjects' Responses. In the informed consent form, subjects are told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff with the possible exception of State or Federal regulatory personnel for audits. All records are kept in locked files. Each subject is given a code number for database purposes, and the patient's name does not reside in the database. Computer files will be stored in a database that is password protected and behind an institute and department firewall. No one but the project staff has access to the master list linking subjects' names to code numbers, and all information obtained is coded. The master list is kept under strict lock and key. The research data on specific measures are released to the patients, and this is specified in the consent form. A certificate of confidentiality has been obtained from the NIH.
Will the study be conducted under a certificate of confidentiality?
Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects

Patients will obtain free clinical evaluation, neuropsychological testing, and may benefit from treatment with Lithium or placebo. The treatment is clinically not inconsistent with treatment typically received by patients with AD who develop agitation with or without psychosis.

Potential benefits to society may be considerable. If the hypotheses are supported by the results, this will suggest that lithium may be a useful alternative or adjunct to the use of other psychotropic medications to treat agitation with or without psychosis in AD.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Compensation will include $20.00 per hour spent in the clinic during study visits. We may also reimburse for travel expenses, if needed by the subject.

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