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Citalopram for agitation in Alzheimer's disease (CitAD): design and methods

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Abstract

Background—Agitation is one of the most common neuropsychiatric symptoms of Alzheimer's disease (AD), and is associated with serious adverse consequences for patients and caregivers. Evidence-supported treatment options for agitation are limited. The citalopram for agitation in Alzheimer's disease (CitAD) study was designed to evaluate the potential of citalopram to ameliorate these symptoms.

Methods—CitAD is a randomized, double-masked, placebo-controlled multicenter clinical trial with two parallel treatment groups assigned in a 1:1 ratio and randomization stratified by clinical center. The study has eight recruiting clinical centers, a chair's office and a coordinating center located in university settings in the United States and Canada. 200 people having probable Alzheimer's disease with clinically significant agitation and without major depression are being

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recruited. Patients are randomized to receive citalopram (target dose of 30 mg/day) or matching placebo. Caregivers of patients in both treatment groups receive a structured psychosocial therapy. Agitation will be compared between treatment groups using the NeuroBehavioral Rating Scale and the AD Cooperative Study- Clinical Global Impression of Change which are the primary outcomes. Functional performance, cognition, caregiver distress and rates of adverse and serious adverse events will also be measured.

Conclusion—The authors believe the design elements in CitAD are important features to be included in trials assessing the safety and efficacy of psychotropic medications for clinically significant agitation in Alzheimer's disease.

Keywords

Alzheimer dementia; citalopram; agitation; randomized trial

1. Introduction

Alzheimer's disease (AD) is a global public health concern whose hallmark is progressive cognitive and functional decline [1]. Neuropsychiatric symptoms (NPS) are common in AD, affecting almost all patients over the course of the illness [2–7]. Agitation is an important and particularly serious NPS which involves emotional distress, excessive psychomotor activity, aggressive behaviors, irritability and disinhibition. Over the 5-year follow-up of the Cache County study, 42% of dementia participants developed agitation [8]. Agitation is a chronic problem for patients at all levels of dementia severity [6,9,10] resulting in impaired quality of life, caregiver burden, dangerous behaviors, institutionalization, restraint use, and psychiatric admission [11]. Therefore the management of agitation is a major priority in caring for people with AD.

Despite the clinical impact of agitation in dementia, an ideal treatment has not been found and options remain limited. A systematic review of 162 studies of non-pharmacologic approaches to managing NPS in dementia concluded that there is evidence, based primarily on uncontrolled or single-blind trials, for the effectiveness of caregiver education and caregiver- or patient-oriented behavioral management techniques [12]. Benefits were typically limited to milder forms of agitation. Psychological approaches, even if feasible to implement, do not preclude the use of adjunctive pharmacologic treatment. In terms of pharmacological management, the most studied medication classes have been antipsychotics (APs), both conventional and atypical, which are often the first-line treatment for management of agitation in AD. Several randomized clinical trials (RCTs) have demonstrated the utility of conventional agents [2,3,7,13] and atypical APs [14,15]. However these agents have significant risks associated with their use including weight gain, dyslipidemia, blood glucose dysregulation, orthostasis, extrapyramidal side effects, prolonged QTc-interval on the electrocardiogram, drowsiness, peripheral edema, cerebrovascular events and mortality [15–18]. The risk of mortality also increases with treatment duration and decreases with treatment cessation, demonstrated in one trial which found significantly higher 12-month mortality for nursing home patients with AD who continued on APs versus those who discontinued APs [19] though observations from a few naturalistic nursing home surveys have not shown a higher mortality rate for patients receiving APs [20–22]. Overall, evidence of efficacy for all types of antipsychotics for agitation in dementia is at best modest, and given concerns about the safety profile, it is not clear that their risk to benefit ratio warrants their use as a first-line treatment in most cases [14,15]. Other medications have been assessed for agitation in AD primarily from post-hoc analyses, including anxiolytics, anticonvulsants, cholinesterase inhibitors and memantine and most have demonstrated equivocal utility for agitation, an adverse risk-benefit ratio and

significant drug-drug interactions [23–25]. Thus further trials and alternative treatment avenues are needed.

Neuropathological [26–30], neuroimaging [31,32] and genetic polymorphism studies [29,33–35] have implicated serotonergic nuclei and serotonin loss as potentially playing a role in the agitation seen in AD. Preliminary studies also support the role of selective serotonin reuptake inhibitors (SSRIs) in the treatment of agitation in AD. Investigators of a Nordic multicenter study found that Alzheimer's patients treated with citalopram showed greater improvements in irritability and restlessness than those taking placebo [36]. Simlarly, Nyth, et al., found improvements in agitation in those taking citalopram to be greater than placebo in elderly patients with depression [37], and in an uncontrolled study, Ragneskog, et al., reported a reduction in irritability, anxiety and restlessness in elderly patients taking citalopram [38]. More recently, Pollock and colleagues demonstrated the utility of citalopram for behavioral disturbances in dementia in a short-term, unmasked study, with improvements in disinhibition, agitation, hostility and suspiciousness [39]. In a randomized, placebo-controlled follow-up study, citalopram was compared to placebo for management of behavioral disturbances in non-depressed agitated dementia patients [40]. Citalopram, compared to placebo, significantly reduced total Neurobehavioral Rating Scale (NBRS) scores; significant improvement in agitation specifically was seen only with citalopram. Subsequently, in the Continuing Pharmacotherapy for Agitation in Dementia study (CPAD), Pollock and colleagues compared citalopram and risperidone in a 12-week RCT of 103 agitated dementia inpatients. For the primary outcome measure, citalopram was associated with a 13% decrease in agitation versus 8% for risperidone, and had a lower side effect burden [39]. Thus, citalopram has shown potential for efficacy in treating agitation in dementia, but the preliminary data require replication specific to an AD population in a larger randomized controlled trial.

2. Methods

2.1 Study organization

CitAD is an investigator-initiated clinical trial funded by the National Institute on Aging (NIA) with additional funding provided by the National Institute of Mental Health (NIMH). The study has eight recruiting clinical centers and two resource centers (the chair's office and the coordinating center) which are listed in Table 1. The primary decision-making body of CitAD is its Steering Committee, a body of investigators representing each of the clinical and resource centers. The Steering Committee is responsible for making decisions regarding design issues, study procedures, allocation of study resources, priorities for meeting the competing demands of the study as well as the review of study progress and study publications.

The Data Safety and Monitoring Board (DSMB) includes voting and non-voting members. The three voting members of the DSMB are appointed by the study chair and have expertise in the fields of biostatistics, psychiatry and neurology. They are independent of the conduct of CitAD and are charged with protecting the interests of CitAD participants via unmasked review of accumulating data on the safety and efficacy of citalopram compared to placebo. The DSMB reports its recommendations to the Steering Committee. The Steering Committee reviews and votes on any recommendations made by the DSMB. The non-voting members of the DSMB are representatives of study leadership that are able to address various aspects of the conduct of the trial, including protocol implementation and data analysis.

2.2 Recruitment, eligibility and consent

Study participants are recruited from memory clinics, geriatric psychiatry clinics, Veterans Administration geriatric clinics, nursing homes, community outreach, advertising and Alzheimer Research Centers associated with the seven US and one Canadian clinical centers. CitAD participants have probable Alzheimer's disease as defined by NINCDS-ADRDA [41] criteria with Mini-Mental State Examination (MMSE) [42] scores of 5–28 inclusive; the dementia diagnosis requires review from study leadership before enrollment for those potential participants with a MMSE score of 27 or 28. Participants also have "clinically significant agitation" for which a physician has determined that a medication is appropriate and that is rated as 1) occurring 'very frequently' or 2) occurring 'frequently' with 'moderate' or 'marked' severity as assessed by the agitation/aggression items of the Neuropsychiatric Inventory (NPI) [43]. In addition, the participants do not meet criteria for Major Depressive Episode by DSM-IV (TR) [44]. Each CitAD participant must have a study partner who spends several hours a week with the patient, supervises the participant's care, and accompanies the participant to all study visits. The detailed list of eligibility criteria for CitAD is given in Table 1.

Prospective participants are first assessed for their ability to provide informed consent. The participants' capacity to give consent is assessed in clinical interviews by clinicians experienced in clinical dementia research. Consent is obtained if the participant is found to be capable of providing consent. If the participant is not fully capable of providing consent then consent is obtained from an authorized legal representative and the participant is asked to provide assent. Consent is obtained using procedures established by the clinical centers and their overseeing Institutional Review Board (IRB) or Research Ethics Board (REB) in accordance with local law. Consent is also obtained from the study partners that accompany the participants on study visits, as they will be providing data on themselves as caregivers of the participants. The study protocol was reviewed and approved by the IRB or REB at each clinical center and the coordinating center.

2.3 Randomization and masking

Participants are randomized in a 1:1 ratio to receive citalopram or matching placebo. The treatment assignment schedule was created by the coordinating center using a documented, auditable SAS program (SAS/STAT® software, Version 9.1 of the SAS System for Windows; Copyright © 2000–2004 SAS Institute Inc, Cary NC, USA) and was generated in blocks of permuted length and stratified by clinical center. Clinical centers request treatment assignments using an online program accessible via the CitAD data system. After confirmation of eligibility, the treatment assignment is given in the form of a medication kit ID. The corresponding medication kits are packaged by the Johns Hopkins Bayview Medical Center Pharmacy to contain either citalopram or placebo according to the treatment assignment schedule and are labeled by medication kit ID only. Treatments are administered in a double-masked fashion; participants, their caregivers and clinical center personnel are all masked to treatment assignment. Masking is accomplished by over-encapsulating citalopram tablets and creating matching placebos both backfilled with microcrystalline cellulose into opaque capsules.

2.4 Treatment protocol

The target dose of citalopram in CitAD is 30 mg/day provided as a single dose in the morning, as this has been well tolerated in the preliminary studies. A starting dose of 10 mg is titrated up over 2 weeks to 30 mg daily. The dose can then be decreased to 10 mg daily depending on tolerability. Lorazepam (0.5 mg daily) is permitted as a rescue medication for clinically significant agitation. Trazodone (≤ 50 mg nightly) is also allowed to treat sleep disturbance for patients with clinically significant sleep disturbance.

The study investigators believe that the use of placebo is acceptable for two reasons. First, only one placebo-controlled efficacy study for treating agitation in AD dementia with citalopram has been conducted [40]. While citalopram was found to be efficacious compared to placebo, the study had a small sample size and included patients with a range of NPS. Additionally, agitation can be stabilized in the short term with the use of adjunctive lorazepam. Given the safety lessons learned from the ongoing use of antipsychotics in dementia, a placebo arm allows for a thorough and systematic assessment of the safety of citalopram in this specific patient population.

2.5 Psychosocial intervention

We use a psychosocial intervention in this trial to ensure that all study patients and caregivers receive appropriate standard of care from study personnel. We believe that this approach both aids in recruitment and complies with the Declaration of Helsinki amendment regarding placebo-controlled trials. This intervention is designed to be practical for the clinical setting and readily standardized for the research setting to limit potentially variable effects of individual site interactions with the study subject and caregivers.

All study caregivers and patients (when possible) regardless of treatment assignment will receive the CitAD standardized psychosocial intervention, which consists of three components: a 20 – 30 minute counseling session at each of the scheduled study visits, provision of educational materials, and 24-hour availability for crisis management assistance.

The counseling sessions are conducted by a trained study clinician and include design of a supportive care plan during the randomization visit. Counseling sessions include:

- Review and adjustment of the patient and caregiver supportive care plan;
- Emotional support and an opportunity to ventilate feelings;
- Counseling regarding specific caregiving skills;
- Assistance with problem-solving of specific issues brought up by the caregiver or study participant;
- Discussion of the educational materials (*The 36-Hour Day* [45] and the *Johns Hopkins Dementia Care Guidelines for Caregiver* [1]).

2.6 Outcome measures

Primary agitation measures are the agitation subscale of the Neurobehavioral Rating Scale (NBRS) [46] and the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change in agitation (ADCS-CGIC). The NBRS is a 28-item observer-rated instrument derived from the Brief Psychiatric Rating Scale (BPRS). The agitation subscale includes the NBRS items regarding disinhibition, agitation and hostility/uncooperativeness and was used as an agitation outcome in the preliminary studies [39,40]. The ADCS-CGIC [47] was developed to assess clinically significant change in AD clinical trials, and focuses on change since baseline. Using an approach similar to the one used in the Depression in Alzheimer's Disease Study-2 (DIADS-2) [48], the ADCS-CGIC has been modified by the addition of items specific to agitation in AD thus producing a global rating of change in agitation over time by a trained clinician. Agitation over nine weeks as measured by the NBRS and change in agitation syndrome from baseline as measured by the ADCS-CGIC are both primary efficacy outcome measures.

Secondary efficacy outcome measures include the Neuropsychiatric Inventory (NPI) [43], Cohen-Mansfield Agitation Inventory (CMAI) [49] and cumulative lorazepam dose as a

marker of breakthrough agitation. The NPI is the most widely used measure of NPS in dementia clinical trials. In CitAD, the NPI will be used for three purposes: (1) the NPI agitation domain ratings will be used as an entry criterion to define moderate or more severe agitation; (2) the NPI domain ratings (overall and agitation specific ratings) from baseline to 9 weeks will be compared between the treatment groups; (3) the NPI caregiver distress ratings from baseline to 9 weeks will be compared by treatment group. Since we expect a notable number of the CitAD patients to reside in nursing homes, we will also administer the CMAI, which was developed for use in nursing homes to observe agitated behaviors in the elderly [49]. The CMAI scores will be compared from baseline to 9 weeks between the treatment groups. Since we expect the functional status of patients to improve with improvements in agitation, we will also compare the treatment groups with respect to the Alzheimer Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) [50] which is an ADL inventory developed to measure functional performance in people with AD. Important secondary safety outcomes include the Mini-Mental State Examination (MMSE) [42] which will be used to compare dementia severity, the Get Up and Go (GUG) [51] which will be used to compare mobility and gait, as well as rates of adverse events.

Plasma samples for citalopram will be obtained at weeks 3, 6, and 9 and the time of sample and reported time of last dose will be recorded in order to assess drug exposure in a population pharmacokinetic (PK) analysis.

2.7 Data collection

All patients are followed via in-person study visits and telephone contacts even if no longer adherent to the assigned study treatment. Scheduled visits occur at enrollment and weeks 3, 6 and 9 following enrollment. Scheduled telephone contacts occur at weeks 1, 2, 4.5 and 7.5 weeks following enrollment. The data collection schedule is detailed in Table 2. Unscheduled visits or telephone contacts will be used as needed to provide medical monitoring, encourage compliance, or offer counseling and behavioral interventions.

Data are collected using paper forms and keyed by study personnel at the clinical centers into the CitAD data system. The data are stored in redundant databases residing on a password protected web server and archived daily at the coordinating center. The data entry application contains error and consistency checks, and the coordinating center conducts audits of clinical center data throughout the course of the trial.

2.8 Treatment unmasking

Unmasking occurs routinely for all participants at the week 9 visit after the required data collection is complete, therefore enabling participants exiting the trial to make informed decisions about continued treatment. The identity of the treatment assignment is provided by the coordinating center to clinical center personnel who then convey it to the patient and caregiver. Emergency unmasking before the week 9 visit is expected to be rare and is allowed only in emergency situations, such as accidental overdose, and not for the medical management of potential adverse effects. Adverse effects are managed under the assumption that patients are receiving citalopram and study treatment may be terminated for unacceptable presumed adverse effects without unmasking the treatment assignment.

2.9 Definition of comparisons, analyses and power calculations

Definition of primary comparisons—The primary assessment of efficacy will be based on the intention-to-treat comparison of the longitudinal NBRS agitation outcomes *over the 9 weeks* and the comparison *at week 9* of the ratings for the agitation domain of the ADCS-CGIC. The hypotheses for these comparisons are of superiority, i.e., we expect that the citalopram group will have lower NBRS scores than the placebo group (corresponding to

less agitation) over the course of 9 weeks. We also expect the proportion of patients with scores indicating worse agitation at week 9 (compared to baseline) on the ADCS-CGIC will be lower on citalopram than placebo.

Analysis of NBRS—The NBRS will be assessed at baseline and weeks 3, 6, and 9. Longitudinal analyses of NBRS scores to compare treatment groups over time will be conducted using a linear mixed effects model with random intercept and slope for each participant.

Analysis of ADCS-CGIC—Ratings on the ADCS-CGIC at week 9 will be compared between treatments. In order to capitalize on the ordered categories of the ADCS-CGIC (ranging from 1 = marked improvement to 7 = marked worsening, with a score of 4 representing no change), proportional odds regression will be used. This method assumes the odds ratios are constant across the response categories. Although this assumption may not be precisely met, this method has the correct type I error rate under the null hypothesis of no treatment effect. Moreover, this method offers substantial gains in efficiency relative to a binary analysis where one collapses the outcome measure into two categories (e.g., improvement versus no improvement) [52].

Analysis of secondary outcomes—Analyses will also be conducted on the CMAI scores as well as the domain ratings of the NPI over weeks 3, 6, and 9 using longitudinal analyses as described above. The total dose of “rescue” lorazepam used between visits will be recorded at weeks 3, 6 and 9 and compared using linear regression. Other secondary outcomes to be examined by treatment group include global cognition (MMSE), activities of daily living (ADCS-ADLs), time and performance on the GUG, rates of adverse events, and discontinuation of study treatment.

Power calculations—Power calculations were made for the two primary hypotheses. Information needed to calculate the power for the NBRS agitation outcome was obtained from a preliminary study.[40] The preliminary information and the desired clinical difference were used to simulate the expected distribution of the data and determine the parameters of a linear mixed effects model with random intercept and slope [53], with which we predicted the likely covariance structure and expected averages at baseline and weeks 3, 6 and 9 for each treatment group. We then calculated the power to detect differences in the simulated distributions. With an enrollment of 200 participants (1:1 allocation ratio), the power to detect a 3 to 5 point difference on the NBRS is at least 85% assuming a two-sided type I error of 5%. A difference of this magnitude was determined to be realistically attainable based on the data from the preliminary study and thought to be clinically meaningful by the members of the Steering Committee after discussion at an investigators’ meeting.

To calculate the power for the ADCS-CGIC outcome, standard two sample power estimations for comparing two proportions were used. The assumption made was that 20–30% of participants assigned to placebo will improve considerably (i.e., will be rated as showing moderate or marked improvement) based on data from antipsychotic agitation in AD trials [14]. With 200 participants, the study will have greater than 80% power to detect a difference of 20% between the proportion of participants who improve (or worsen) in the citalopram group compared to the placebo group. This binary power calculation can be taken as a lower bound of the power for the proportional odds analysis described above.

2.10 Quality assurance

Physicians, coordinators and nurses were trained in the uniform use of all assessment instruments and tested for knowledge of study protocol and procedures prior to the enrollment of participants. The training will be reinforced during annual research group meetings. Training methods include didactic instruction and clinical demonstrations. In addition, standardized methods for performing study procedures are detailed in the study handbook. The performance of the clinical centers is monitored continually via review of many performance criteria including (but not limited to) enrollment, completed and missed visits, losses to follow-up, protocol deviations, and data edit queries. The coordinating center performs site visits at each of the clinical centers to review the study documentation, consent forms, IRB submissions and approvals, staffing, forms and data management and study drug accounting. The DSMB monitors the accumulating data for clinical center performance as well as safety and efficacy on an annual schedule.

3. Discussion

3.1 A new class of agents for agitation: SSRIs?

Agitation in AD is a serious clinical problem and several pharmacological and non-pharmacological interventions have been previously studied. Non-pharmacological interventions have not been proven effective for moderate or more severe agitation. Whereas studies have suggested that atypical antipsychotics may have a role, concerns about safety and tolerability limit their utility. Serotonergic dysfunction has been associated with agitation in patients with AD [30,31,33] and early clinical trial findings suggest that SSRIs are a reasonable approach for the treatment of agitation in this population. While they are widely prescribed for use in patients with AD, their efficacy and safety when used to treat agitation has not been fully established. In addition to efficacy measures, CitAD is designed to assess a range of relevant clinical and laboratory data to provide detailed safety information about citalopram for patients with AD and agitation.

3.2 Defining agitation for this and future trials

There is no gold standard for assessing the presence of agitation in dementia, or its response to treatment. In CitAD we have chosen to use a pragmatic approach to define clinically significant agitation using the judgment of experienced clinicians combined with severity ratings above a cutoff indicative of moderate or more severe agitation on the NPI. Regarding the assessment of treatment response, changes in rating scale total scores may not reflect marked changes in specific domains, the significance of which may be lost in a modest decrease in overall score. In CitAD ratings over time on the validated NBRS scale [54,55] are being combined with a global rating in which the specific domains of agitation, dishinhibition/aggression and hostility/uncooperativeness are weighed over time by study clinicians masked to treatment assignment. A similar combined approach of a global rating with a symptom scale was used successfully in a trial for depression in Alzheimer’s disease [56,57].

3.3 Assessing citalopram with psychosocial intervention, lorazepam and dementia medications

Disentangling the treatment effects from competing effects on the outcome is always a concern. Specifically in CitAD, we will be assessing the effect of citalopram in the presence of a psychosocial intervention, concomitant lorazepam and/or trazodone use, and prescribing of “anti-dementia” medications such as cholinesterase inhibitors and memantine.

Select psychosocial interventions targeted at the caregivers of dementia patients have been shown to have beneficial effects on NPS [12]. The clinical centers involved in CitAD

provide elements of such interventions to their patients and caregivers as part of their standard of care. Psychosocial intervention will likely improve agitation in participants in both treatment groups, making it more difficult to distinguish treatment effects. However we have an ethical imperative to provide all study participants with interventions that have been shown to be effective. The important question of interest is whether we can improve agitation with citalopram above the improvement seen with standard of care techniques.

Memantine and cholinesterase inhibitors have the potential to affect cognition and functioning. However, these drugs are not likely to improve or worsen agitation and should not complicate the assessment of main outcome [58,59]. Most eligible dementia patients will be on one or more of these medications; not allowing participants to take Alzheimer's medications would limit generalizability and hamper recruitment. However, we do require that patients be on a stable dose of these medications for one month prior to randomization. We expect the proportion of patients on cholinesterase inhibitors and memantine at baseline to be similar in the two treatment groups due to randomization.

Since enrolled patients will be fairly agitated, study physicians will be allowed to administer adjunctive lorazepam in the lowest possible dose and not more than 0.5 mg/day. The use of lorazepam is expected to facilitate the de-escalation of agitation after randomization and serve as an incentive for patients and caregivers to continue participation. However, the use of concomitant lorazepam has the potential to bias the estimate of the citalopram treatment effect on agitation if the use is differential by treatment group. Lorazepam use will be monitored in both treatment groups and the cumulative lorazepam dose will be analyzed by treatment group.

3.4 Timeframe – why nine weeks?

The study is designed for 9 weeks of masked treatment. Preliminary studies [40] demonstrate treatment benefits as early as three weeks after initiation. However, it is unclear whether such effects will be maintained past this period. It is important to evaluate treatment effects over a longer time frame. Data from preliminary studies and experience with citalopram as an antidepressant suggest that its beneficial effects will become manifest within a 4–8 week time frame. Therefore, we propose to monitor participants for 9 weeks after randomization.

3.5 Treatment effects on other outcomes

Citalopram therapy may ameliorate some portion of AD-related impairment in cognitive functioning and in difficulties with activities of daily living through improvement in mood and non-mood symptoms. Furthermore, since increased agitation adds to the burden of the caregivers of those with AD, treatment with antidepressants has the potential to benefit those who care for AD patients. CitAD will serve as an efficient setting for addressing these secondary hypotheses and for exploring the interrelationships between these outcomes.

3.6 How CitAD will move the field forward

The CitAD study builds on the clinical and research experience of this collaborative group of investigators, especially as it relates to the design and execution of DIADS-2. Several of the design elements, such as the modified ADCS-CGIC, the standardized psychosocial intervention, duration of the placebo-controlled phase, frequent telephone contacts between scheduled visits, unmasking the treatment assignment immediately at the end of the study and assessment of drug exposure through the pharmacokinetic analysis are important features to be included in trials of agitation in patients with AD and will hopefully rekindle and move forward intervention studies for this and other behavioral disturbances in dementia.

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Table 1

Design Summary

Citalopram for Agitation in Alzheimer's disease (CitAD)
Objectives
Primary objective
To examine in a masked, randomized trial the efficacy of citalopram for the treatment of clinically significant agitation, without depression, in patients with Alzheimer's dementia
Secondary objectives
To examine the effects of citalopram treatment on function and cognition of patients as well as caregiver distress
To examine the safety of citalopram
To examine predictors of response to citalopram therapy
Type of trial
Randomized, multicenter clinical trial
Two parallel treatment groups
Double masked
1:1 assignment ratio
Setting
Clinical centers
Columbia University Medical Center
Johns Hopkins School of Medicine
Medical University of South Carolina
Stanford University School of Medicine
University of Pennsylvania School of Medicine
University of Rochester School of Medicine
University of Southern California Keck School of Medicine
University of Toronto
Chair's office
Johns Hopkins School of Medicine
Coordinating center
Johns Hopkins Bloomberg School of Public Health
Primary outcome measures
Agitation over 9 weeks as measured by NBRS
Change in agitation as measured by ADCS-CGIC
Other outcomes
Agitation over 9 weeks as measured by CMAI
Agitation over 9 weeks as measured by NPI agitation sub-items
Cumulative lorazepam dose
Functional performance as assessed by ADCS-ADL
Cognition as assessed by MMSE
Caregiver distress as assessed by caregiver distress ratings on NPI

Citalopram for Agitation in Alzheimer's disease (CitAD)
Adverse events and serious adverse events
Study population
200 patients who meet the CitAD criteria for clinically significant agitation
Power calculations
NBRS agitation subscale: Power greater than 85% Two-sided alpha = 0.05 Detectable difference in reduction of agitation severity is 40% (i.e., 3 to 5 point difference on the NBRS) ADCS-CGIC agitation domain: Power greater than 80% Two-sided alpha = 0.05 Assuming 20–30% of placebo patients improve Detectable difference in proportion of patients improving is 20%
Treatment groups
Citalopram, target dose 30 mg per day (range 10–30 mg per day), given orally + standardized psychosocial intervention Placebo + standardized psychosocial intervention
Stratification of randomization
By clinical center
Masking
Double-masked (treatment assignment masked to participants and all clinical center personnel, including physicians, nurses, and neuropsychologists)
Inclusion criteria
Probable Alzheimer's disease (NINCDS-ADRDA criteria), with MMSE score of 5–28 inclusive Medication for agitation is appropriate, in the opinion of the study physician Clinically significant agitation for which either 1. the frequency of agitation as assessed by the NPI is 'Very frequently', or 2. the frequency of agitation as assessed by the NPI is 'Frequently' AND the severity of the agitation as assessed by the NPI is 'Moderate', or 'Marked' Provision of informed consent for participation in the study by patient or surrogate (if necessary) and caregiver Availability of primary caregiver, who spends several hours a week with the patient and supervises his/her care, to accompany the patient to study visits and to participate in the study No change to AD medications within the month preceding randomization, including starting, stopping, or dosage modifications
Exclusion criteria
Meets criteria for Major Depressive Episode by DSM-IV (TR) criteria Presence of a brain disease that might otherwise explain the presence of dementia, such as extensive brain vascular disease, Parkinson's disease, dementia with Lewy bodies, traumatic brain injury, or multiple sclerosis Psychosis (delusions or hallucinations *requiring antipsychotic treatment* in the opinion of the study physician) Treatment with citalopram is contraindicated in the opinion of the study physician Failure of past treatment with citalopram for agitation after adequate trial at a minimally accepted dose (≥20mg/day) Treatment with a medication that would prohibit the safe concurrent use of citalopram, such as MAO inhibitors

Citalopram for Agitation in Alzheimer's disease (CitAD)
Need for psychiatric hospitalization, or is suicidal
Current participation in a clinical trial or in any study that may add a significant burden or affect neuropsychological or other study outcomes
Current treatment with antipsychotics, anticonvulsants (other than dilantin), other antidepressants (other than trazodone, ≤50 mg per day at bedtime), benzodiazepines (other than lorazepam), or psychostimulants
Any condition that, in the opinion of the study physician, makes it medically inappropriate for the patient to enroll in the trial
Duration of follow-up
9 weeks
Data collection schedule
Scheduled in-person visits (weeks 3, 6, and 9 after randomization)
Telephone contacts (weeks 1, 2, 4.5, and 7.5 after randomization)

Table 2

Data collection schedule

	Assessment visits and contacts (weeks from enrollment)*							
	0	**1**	**2**	**3**	**4.5**	**6**	**7.5**	**9**
Procedures								
Consent	✓	✓	✓	✓	✓	✓	✓	✓
History, or interim history	✓	.	.	✓	.	✓	.	✓
Vital signs, ongoing medical monitoring	✓	.	.	✓	.	✓	.	✓
Blood								
DNA	✓	.	.	.	.	.	.	.
Electrolyte panels	✓	.	.	✓	.	✓	.	✓
Citalopram levels	.	.	.	✓	.	✓	.	✓
Review of compliance	.	.	.	✓	.	✓	.	✓
Review of medication use	.	✓	✓	✓	✓	✓	✓	✓
Review inclusion/exclusion	✓	.	.	✓	.	✓	.	✓
Review of adverse events	.	✓	✓	✓	✓	✓	✓	✓
Dispensing of study drug	✓	.	.	✓	.	✓	.	.
Patient assessments								
NBRS	✓	.	.	✓	.	✓	.	✓
ADCS-CGI	✓	.	.	✓	.	✓	.	✓
CMAI	✓	.	.	✓	.	✓	.	✓
CSDD	✓	.	.	.	.	.	.	.
NPI	✓	.	.	✓	.	✓	.	✓
NPI (agitation domain only)	.	✓	✓	.	✓	.	✓	.
ADCS-ADL	✓	.	.	✓	.	✓	.	✓
MMSE	✓	.	.	✓	.	✓	.	✓
GUG	✓	.	.	✓	.	✓	.	✓
Caregiver intervention								
Psychosocial intervention	✓	.	.	✓	.	✓	.	✓

NBRS, NeuroBehavioral Rating Scale, ADCS-CGI, Alzheimer's Disease Cooperative Study - Clinical Global Impression; CMAI, Cohen-Mansfield Agitation Inventory; CSDD, Cornell Scale for Depression in Dementia; NPI, Neuropsychiatric Inventory; ADCS-ADL, Alzheimer's Disease Cooperative Study - Activities of Daily Living; MMSE, Mini-mental State Examination; GUG, Get up and Go

* In-person clinic visits occur at enrollment and weeks 3, 6 and 9 following enrollment. Telephone contacts occur at weeks 1, 2, 4.5 and 7.5 following enrollment.