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Effect of Citalopram on Agitation in Alzheimer's Disease – The CitAD Randomized Controlled Trial

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Abstract

Importance—Agitation is common, persistent, and associated with adverse consequences for patients with Alzheimer's disease (AD). Pharmacological treatment options, including antipsychotics are not satisfactory.

Objective—The primary objective was to evaluate the efficacy of citalopram for agitation in patients with AD. Key secondary objectives examined effects of citalopram on function, caregiver distress, safety, cognitive safety, and tolerability.

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The authors designed the study, vouch for the completeness and accuracy of the data, carried out the analyses and wrote the manuscript.

Design, Setting and Participants—The Citalopram for Agitation in Alzheimer's Disease Study (CitAD) was a multicenter, randomized, placebo-controlled, double-blind, parallel group trial that enrolled 186 patients with probable AD and clinically significant agitation from eight academic centers in the US and Canada from August 2009 to January 2013.

Interventions—Participants (n=186) were randomized to receive a psychosocial intervention plus either citalopram (n=94) or placebo (n=92) for 9 weeks. Dose began at 10 mg/d with planned titration to 30 mg/d over 3 weeks based on response and tolerability.

Main Outcomes and Measures—Primary outcome measures were the Neurobehavioral Rating Scale, agitation subscale (NBRS-A) and the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC) Other outcomes were the Cohen-Mansfield Agitation Inventory (CMAI), Neuropsychiatric Inventory (NPI), activities of daily living (ADLs), caregiver distress, cognitive safety (MMSE), and adverse events.

Results—Participants on citalopram showed significant improvement compared to placebo on both primary outcome measures. NBRS-A estimated treatment difference at week 9 (citalopram minus placebo) was −0.93 [95% CI: −1.80 to −0.06], p = 0.036. mADCS-CGIC results showed 40% of citalopram participants having moderate or marked improvement from baseline compared to 26% on placebo, with estimated treatment effect (odds ratio of being at or better than a given CGIC category) of 2.13 [95% CI 1.23 to 3.69], p = 0.007. Participants on citalopram showed significant improvement on the CMAI, total NPI and caregiver distress scores but not on the NPI agitation subscale, ADLs, or in less use of rescue lorazepam. Worsening of cognition (−1.05 points [95% CI: −1.97 to −0.13], p = 0.026) and QT interval prolongation (18.1 ms [95% CI: 6.1, 30.1], p = 0.004) were seen in the citalopram group.

Conclusions and Relevance—Among patients with probable Alzheimer's disease and agitation receiving psychosocial intervention, the addition of citalopram compared with placebo significantly reduced agitation and caregiver distress, but cognitive and cardiac adverse effects of citalopram may limit its practical application at the 30 mg/d dose studied in this trial.

Introduction

Neuropsychiatric symptoms occur in a majority of patients with Alzheimer's disease (AD). Agitation refers to emotional distress, excessive psychomotor activity, aggressive behaviors, disruptive irritability, and disinhibition. Agitation is common, persistent, difficult to treat, costly, and associated with severe adverse consequences for patients and caregivers[1–5]. Psychological, environmental and pharmacologic therapies have proven inadequate. Antipsychotics continue to be widely used for agitation, despite serious safety concerns, including increased mortality, and uncertain efficacy[5–10].

Citalopram, a selective serotonin reuptake inhibitor (SSRI), is frequently used in older individuals[11–12] and has been suggested as an alternative to antipsychotic drugs for agitation and aggression in dementia[13–16]. Yet, there is limited evidence for its efficacy and safety. In a short-term, unmasked study and two randomized, masked follow-up studies, Pollock and colleagues demonstrated the utility of citalopram for agitation in dementia, but these preliminary data require replication in a larger randomized, double-blind, placebo-controlled trial specific to an AD population[17–19].

The primary objective of the Citalopram for Agitation in Alzheimer's Disease Study (CitAD) was to evaluate the efficacy of citalopram for agitation in patients with AD and without major depression. Secondary objectives were 3-fold: (1) examine the effects of citalopram on patients' functional abilities, and on caregiver distress; (2) examine the safety of citalopram comparing treatment groups on vital signs, weight, gait stability, cognitive effects, side effects, electrolyte panels, adverse event reports, and ECG (added later during the study); and (3) examine predictors of citalopram response. This paper will address the primary objective and item 1 and 2 of the secondary objectives.

Methods

Study Design and Oversight

The CitAD study was an investigator-initiated multicenter, randomized, placebo-controlled, double-blind, two-arm, parallel group trial funded by the National Institute on Aging (NIA) with additional funding provided by the National Institute of Mental Health (NIMH). CitAD enrolled patients from eight academic centers in the US and Canada. The study design including complete eligibility criteria, data collection schedule and detailed statistical analysis was previously reported[20].

CitAD had an independent Data Safety and Monitoring Board (DSMB). The study protocol and amendments were approved by Institutional Review Boards (IRB) or Research Ethics Board (REB) at each clinical center and the coordinating center. Written informed consent was obtained from all participants and informants based on local IRB requirements regarding capacity to consent and surrogate consent. Generic citalopram was purchased and over-encapsulated for use in this study.

All clinical center personnel and participants were masked to treatment assignment. Unmasking occurred routinely at the week 9 visit after data collection was complete, enabling study physicians and participants to make informed decisions about continued treatment[20].

Participants

CitAD participants had probable AD by National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association[21] criteria with Mini-Mental State Examination (MMSE)[22] scores from 5–28 inclusive, and had “clinically significant agitation” for which a physician determined that medication was appropriate and was rated as 1) occurring `very frequently' or 2) occurring `frequently' with `moderate' or `marked' severity on the agitation/aggression domain (one screening question that if answered yes proceeds to 8 subquestions) of the Neuropsychiatric Inventory (NPI)[23]. Participants were excluded if they had a major depressive episode or psychosis requiring antipsychotic treatment. A caregiver who spent at least several hours a week with the patient was required to supervise medications and participate in outcomes assessments. Medications for the treatment of AD (cholinesterase inhibitors and memantine) at stable doses within the month preceding randomization were allowed. Withdrawal of psychotropic medications other than pre-defined rescue medications was required. Adequate

previous treatment or contraindication to citalopram was exclusionary. Prolonged QT interval on ECG was later added as an exclusion criterion (see below). Race and ethnicity were self-reported based on categories defined by the National Institutes of Health.

Interventions

Participants received identically appearing citalopram or placebo capsules allocated in a 1:1 ratio, stratified by clinical center. Target dose of citalopram was 30 mg/day as a single dose in the morning, with planned titration over 3 weeks from a starting dose of 10 mg with subsequent dose changes based on response and tolerability. Lorazepam (0.5 mg daily) and trazodone (≤ 50 mg nightly) were permitted as `rescue' medications for significant agitation or sleep disturbance.

On August 22, 2011, the Food and Drug Administration (FDA) issued an advisory regarding dose-dependent risk of QT prolongation with citalopram therapy[24]. Consequently, the CitAD Steering Committee amended the protocol to exclude individuals with QTc > 450ms for men and >475ms for women at screening, to include an ECG at week 3 and at the visit after dose increase to 30 mg for those on slower titration, and added serum magnesium to routine electrolyte monitoring.

In order to ensure all study patients and caregivers received appropriate standard of care and to limit potentially variable effects of individual site interactions with the participants and caregivers, a trained study clinician conducted a standardized and practical psychosocial intervention consisting of three components: provision of educational materials; 24-hour availability for crisis management; and a 20 – 30 minute counseling session at each of the scheduled study visits including the design of a supportive care plan during the randomization visit, review and adjustment of the supportive care plan at subsequent visits, emotional support and an opportunity to ventilate feelings, counseling regarding specific caregiving skills, and assistance with problem-solving of specific issues brought up by the caregiver or study participant[20].

Outcome measures

Primary efficacy outcome measures were the agitation subscale of the Neurobehavioral Rating Scale (NBRS-A)[25] (range: 0, 18; higher scores indicate more severe symptoms) and the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC)[26] (range 1–7 where 1 indicates marked improvement and 7 indicates marked worsening from baseline). The NBRS-A assesses agitation, hostility/ uncooperativeness, and disinhibition. The clinician-administered mADCS-CGIC was modified to assess items specific to agitation in AD, producing a global rating of change in agitation and a measure of clinical significance.

Secondary efficacy outcomes were the Neuropsychiatric Inventory (NPI)[23](frequency by severity range: 0, 144; higher scores indicate more severe symptoms), individual NPI domain ratings, NPI caregiver distress ratings (range: 0, 60; higher scores indicate more severe distress), Cohen-Mansfield Agitation Inventory (CMAI)[27](range: 14, 70; higher scores indicate more severe symptoms), the Alzheimer Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)[28](range: 0, 78; higher scores indicate better

functioning), and cumulative lorazepam dose. Important secondary safety outcomes included Mini-Mental State Examination (MMSE)[22](range: 0, 30; higher scores indicate better functioning), a measure of cognitive abilities, and the Get Up and Go (GUG)[29], assessing mobility and gait, and elicitation of adverse events using both symptom checklists and open-ended questions.

Statistical Analysis

Primary assessment of efficacy was based on intention-to-treat (ITT) comparison of the difference in the NBRS-A scores at week 9 and comparison at week 9 for the mADCS-CGIC. Crude between-treatment difference at week 9 NBRS-A scores was assessed using a t-test. Adjusted differences were assessed using mixed effects regression models with a random intercept for patient, indicators for each visit, treatment by visit interactions, and covarying for baseline NBRS-A scores and baseline MMSE (due to baseline imbalance). The difference in the linear slope of NBRS-A scores over all study visits was also estimated using mixed effects regression. All available visit data for the 186 participants were incorporated into the NBRS-A model. Other continuous scale scores were modeled in the same way.

We also performed sensitivity analyses for the NBRS-A outcome: 1) using generalized estimating equations (GEE) model for mean visit scores with unstructured covariance structure for within-person longitudinal measurements and robust standard errors for effect estimates[30].

The mADCS-CGIC ratings of change (“marked worsening” to “marked improvement” on a 7 point scale) at week 9 were compared between treatment groups including all participants with week 9 mADCS-CGIC data using proportional odds logistic regression[31]. We performed sensitivity analyses for the mADCS-CGIC outcome by using multiple imputation to estimate missing week 9 data.

The proportion of participants experiencing adverse events was compared between treatment groups using Fisher's exact test for small cells (unadjusted), or logistic regression, adjusting for baseline report of the same symptom if necessary due to baseline imbalance. Adherence was assessed by pill counts from returned medication bottles using the Wilcoxon rank sum test.

Statistical analyses used SAS version 9.2 and R version 2.13.1. All p-values are two-sided and $p < .05$ was the threshold for statistical significance. No adjustments were made for multiple comparisons.

A detailed description of the power calculations has been published[20]. For the NBRS-A, the study was designed to have 85% power to detect a standardized difference at week 9 of 40% for citalopram compared to placebo. For the mADCS-CGIC proportional odds analysis, the study was designed to have power greater than 80% to detect a difference of 20% between citalopram and placebo in the proportions of patients who improve (or worsen).

Results

Patients

186 participants were enrolled between August 2009 and January 2013, 94 assigned to citalopram and 92 to placebo. We intended to enroll 200 participants per protocol by December 31, 2012 but recruitment slowed notably towards the end of this timeframe. Figure 1 summarizes patient recruitment, participation and attrition. Baseline characteristics were similar (Table 1), except participants on placebo had lower mean MMSE scores. Participants were on average in their late 70s, 46% female, two-thirds white and non-Hispanic, community dwelling, and diagnosed with dementia for 5 years. About two-thirds took cholinesterase inhibitors and just over 40% took memantine. Over 90 % of both groups completed the 9 week trial and about 80% remained on treatment. At week 9, 78% of the sample were receiving 30 mg citalopram daily and 15 % were receiving 20 mg citalopram daily.

Primary Outcomes

Participants on citalopram showed significant improvement compared with placebo on both primary outcome measures (Table 2). The raw NBRS-A scores are shown in Figure 2; at week 9 the unadjusted mean scores were 4.1 (SD = 3.0) on citalopram and 5.4 (SD= 3.2) on placebo (crude difference = 1.3 [95% CI: 2.6, 3.5]; p = 0.010). The mixed model estimated difference in week 9 NBRS-A scores for citalopram – placebo was −0.93 [95% CI: −1.80 to −0.06] p = 0.036 (negative numbers favor citalopram). The model estimated differences in scores at the two interim visits were: −0.58 (95% CI: −1.44, 0.29); p = 0.190 at week 3; and −1.12 (95% CI: −1.98, −0.26); p = 0.012 at week 6. The estimated difference in linear slopes over all study visits is −0.12 (95% CI: −0.22, −0.02); p = 0.022. Results for the NBRS-A were virtually identical for the GEE model; the GEE estimated difference in week 9 scores was: −0.94 (−1.80, −0.07); p = 0.033

mADCS-CGIC results showed that 40% of citalopram participants had moderate or marked improvement from baseline severity vs. 26% of placebo participants, with an estimated treatment effect from the proportional odds model including participants with week 9 data (odds ratio of being at or better than a given CGIC category) of 2.13 [95% CI: 1.23 to 3.69], p = 0.007. The estimated OR for the sensitivity analysis including imputed values for missing data was 2.10 [95% CI:1.21 to 3.64].

Secondary Outcomes

Relative to placebo, citalopram was associated with improved scores on CMAI with an estimated difference in week 9 scores of −2.38 [95% CI −4.13 to −0.63], p = 0.008. On the NPI total score, estimated differences for citalopram over placebo in week 9 scores were −6.03 [95% CI: −10.75 to −1.32], p = 0.013; on the NPI agitation subscale, −0.78 [95% CI: −1.77 to 0.21], p = 0.123; and on NPI caregiver distress, −2.70 [95% CI: −4.94 to −0.47], p = 0.018. There was no significant difference between groups on the ADCS-ADL scale. There was no difference between the two treatment groups in the use of rescue lorazepam (Table 2).

Safety and Adherence

There was no difference in adherence between the two study groups. MMSE results showed greater cognitive worsening with citalopram, −1.05 points [95% CI: −1.97 to −0.13], p = 0.026 (Table 2). Anorexia, diarrhea and fever were more common on citalopram and weight loss and insomnia on placebo (Table 3). Falls were more frequent on citalopram, and remained even after controlling for baseline differences. An increase in upper respiratory infections was also noted in the citalopram group. The citalopram group may have shown a slight increase in gait impairment as measured by the GUG, but the rate of hyponatremia did not differ appreciably between the groups. Frequency of serious adverse events was comparable between treatment groups (supplemental table 1). There was one death in the placebo group.

ECG monitoring was initiated after 138 patients were randomized and was available for 48 patients (24 citalopram and 24 placebo). Citalopram was associated with greater increase in QTc interval than placebo, 18.1 ms [95% CI: 6.1, 30.1], p = 0.004, and more participants on citalopram than placebo showed a > 30 ms QTc increase from enrollment to week 3 (7 versus 1; Fisher's exact p = 0.046). Three citalopram and one placebo participants showed QTc prolongation (> 450ms for men and > 475ms for women).

Discussion

Citalopram treatment led to a reduction in agitation in patients with AD. The effect size is clinically relevant: 40% of citalopram-treated participants were judged to be much or very much improved on mADCS-CGIC vs. 26% of those on placebo. Adverse events were generally modest and consistent with known SSRI-mediated adverse events (increases in gastrointestinal complaints, respiratory tract infections, and falls), except that no weight loss or hyponatremia was seen. The cognitive worsening and QT interval prolongation observed in the citalopram group raise concern about the 30 mg/d dose used in this study and may limit the clinical utility of the findings.

Safe and effective treatments for agitation remain elusive with options limited. Patients in this trial had substantial, disruptive behavioral symptoms at the same level or higher than patients with AD who received antipsychotics in the CATIE-AD study,[7, 16] other studies of atypical antipsychotics for dementia,[6] and in trials of donepezil and memantine as primary treatments of agitation[32–33]. Improvement over the course of the trial as measured by total NPI scores was comparable to that of antipsychotics in other trials[6–7, 16] and improvement on the mADCS-CGIC was superior in CitAD. The consistency of outcomes on other scales lends credibility and clinical significance to the trial's outcome that 30 mg/d of citalopram improved agitation. Similar to previous studies we saw a robust rating scales response on placebo[6].

We used the MMSE to monitor for cognitive changes that might be adversely affected by treatment. Greater cognitive decline was seen in the citalopram group over 9 weeks. MMSE scores modestly improved on placebo but worsened on citalopram, with no difference in spontaneously reported somnolence or confusion. The MMSE treatment effect, approximately 1 point, is similar to the mean worsening of 0.73 points with antipsychotics in

similarly designed trials[6] but lower than the minimum clinically significant change of 1.4 points considered by many experts[38]. This finding is consistent with another study reporting declines in verbal learning and psychomotor speed in patients taking citalopram[34], and with prior epidemiological data[35]. Conversely citalopram at 20 mg/d showed significant improvement on the cognitive subscale of the Neurobehavioral Rating Scale (NBRS) in one of the preliminary citalopram studies[18] and the DIADS-2 study indicated that another SSRI, sertraline, neither improved nor impaired cognitive function in patients with depression of Alzheimer's disease[39]. Therefore, while citalopram had a small negative impact on cognitive functioning in this study, its clinical significance is uncertain. Also unknown are whether this cognitive effect continues beyond 9-weeks, and whether citalopram adversely effects the course of AD.

The QT interval prolongation observed here is consistent with the FDA advisory[24] and citalopram's current prescribing information. We maintained a 30 mg/day target dose of citalopram after the FDA advisory and our findings suggest that 30 mg/day in patients with AD should generally be avoided. Current prescribing information recommends a maximum daily dose of 20 mg of citalopram for patients over 60 years of age because of substantially higher exposures, decreased clearance, and prolonged cardiac repolarization potential[37]. Our trial did not have enough patients treated with 20 mg/day to assess the efficacy of that dose.

Strengths of the study include: 1) randomized treatment assignment with inclusion of placebo control; 2) double blind treatment assignment with rigorous adherence to masked rating; 3) high retention rates (>90% over 9 weeks) and adherence to study drug; 4) careful definition of agitation of moderate or higher severity; 5) relatively few medical or medication exclusions resulting in a study population that is broadly representative of AD patients; 6) semi-structured psychosocial intervention administered to all patients and caregivers; 7) consistent results across sites supporting generalizability; 8) consistent findings across multiple measures of agitation and analysis methods.

Limitations of the study include: 1) participants comprised a sample of convenience in US and Canadian academic medical centers that may not generalize to other settings; 2) short duration of treatment; 3) unknown effectof citalopram on agitation in non-AD forms of dementia; 4) unknown effectof citalopram in the more mild and more severe forms of agitation or in inpatient settings; 5) no dose ranging information; 6) baseline differences in the MMSE; 7) absence of more comprehensive assessment of cognition; 8) lack of data collection on potential participants who declined to participate or failed screening.

Conclusion

Identifying drugs outside the antipsychotic class with targeted anti-agitation effects that provide greater benefit or lower risk among patients with Alzheimer's disease is a research priority. While citalopram, at 30 mg daily, was associated with clinically meaningful reduction in agitation in patients with AD over 9 weeks of treatment comparable to what is seen with antipsychotics, citalopram showed mild cognitive and concerning cardiac adverse effects, and cannot be generally recommended as an alternative treatment option at that dose. There are insufficient data, however on efficacy for agitation at lower doses. An assessment of individual patient circumstances, including symptom severity, value of

improvement, cognitive function and change, cardiac conduction, vulnerability to adverse effects, and effectiveness of behavioral interventions can help guide appropriate medication use in patients with marked agitation or aggression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Integrity and Accuracy Statement

Anton P. Porsteinsson and Constantine G. Lyketsos had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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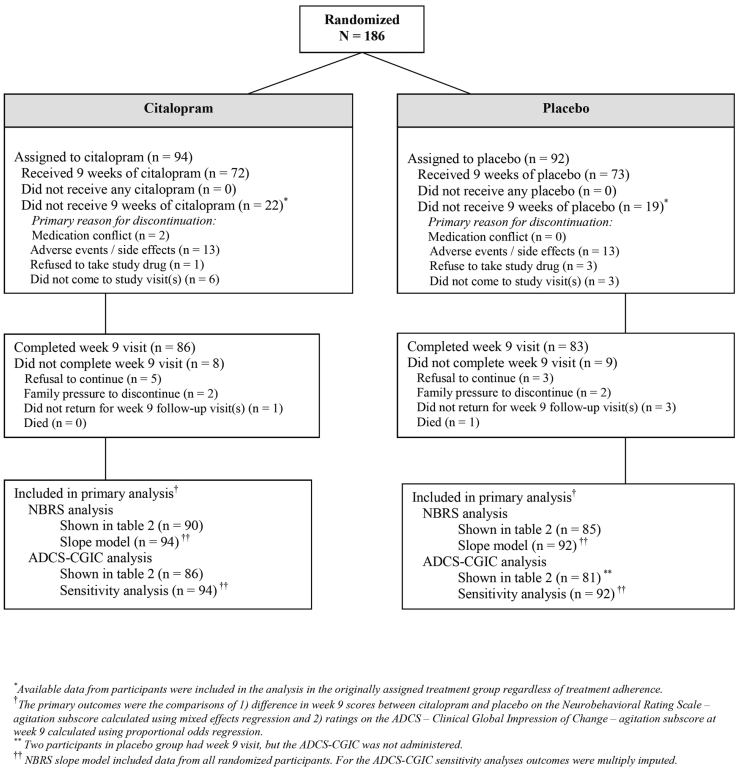

*Available data from participants were included in the analysis in the originally assigned treatment group regardless of treatment adherence.
†The primary outcomes were the comparisons of 1) difference in week 9 scores between citalopram and placebo on the Neurobehavioral Rating Scale – agitation subscore calculated using mixed effects regression and 2) ratings on the ADCS – Clinical Global Impression of Change – agitation subscore at week 9 calculated using proportional odds regression.
**Two participants in placebo group had week 9 visit, but the ADCS-CGIC was not administered.
††NBRS slope model included data from all randomized participants. For the ADCS-CGIC sensitivity analyses outcomes were multiply imputed.

Figure 1.
Participant flow, CONSORT diagram

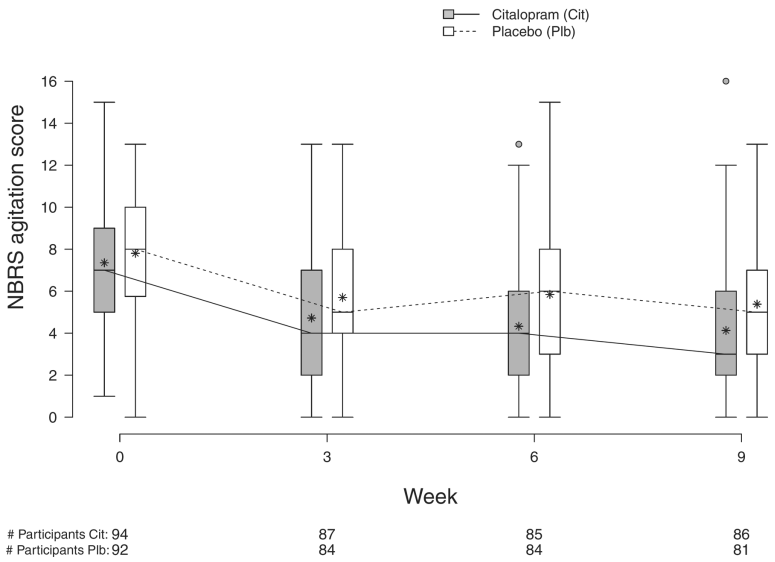

Figure 2. Neurobehavioral Rating Scale (NBRS) – agitation subscore

Higher NBRS scores indicate more severe symptoms. The middle bar of the boxes represents the median; the star in the box represents the mean; the lower and upper ends of the boxes are the first and third quartiles, respectively. The whiskers represent values within 1.5 times the inter-quartile range from the upper or lower quartile (or the minimum and maximum if within 1.5 times the interquartile range of the quartiles) and data more extreme than the whiskers are plotted individually as outliers.

Table 1

Baseline characteristics of the patients

	Total	Citalopram	Placebo
No. randomized	186	94	92
Age in years, mean (SD)	78 (8)	78 (9)	79 (8)
Women, n (%)	85 (46%)	44 (47%)	41 (45%)
Racial / ethnic group, n (%)			
White, non-Hispanic	120 (65%)	62 (66%)	58 (63%)
African-American, non-Hispanic	31 (17%)	15 (16%)	16 (17%)
Hispanic / Latino	24 (13%)	10 (11%)	14 (15%)
Other, non-Hispanic	11 (6%)	7 (7%)	4 (4%)
Highest education, n (%)			
No High school diploma	52 (28%)	25 (27%)	27 (29%)
High school diploma	43 (23%)	20 (21%)	23 (25%)
Some college / associates degree	29 (16%)	18 (19%)	11 (12%)
Bachelor's degree	37 (20%)	21 (22%)	16 (17%)
Professional / graduate degree	25 (13%)	10 (11%)	15 (16%)
Duration of dementia in years, mean (SD)	5 (4)	5 (4)	5 (4)
Concomitant medications, n (%)			
Cholinesterase inhibitors	128 (69%)	62 (66%)	66 (72%)
Memantine	78 (42%)	41 (44%)	37 (40%)
Lorazepam	15 (8%)	6 (6%)	9 (10%)
Trazodone	19 (10%)	11 (12%)	8 (9%)
History of anxiety or mood disorder before AD, n (%)	25 (13%)	11 (12%)	14 (15%)
Neurobehavioral Rating Scale (NBRS) agitation subscore, mean (SD)	7.6 (3.1)	7.4 (3.3)	7.8 (3.0)
Cohen Mansfield Agitation Inventory (CMAI), mean (SD)	28.2 (6.7)	27.7 (6.7)	28.7 (6.7)
Neuropsychiatric Inventory (NPI), mean (SD)			
Total score	37.3 (17.5)	37.3 (17.5)	37.3 (17.7)
Agitation subscore	7.9 (2.3)	7.8 (2.2)	8.0 (2.4)
Depression subscore	2.1 (2.9)	2.2 (3.1)	1.9 (2.7)
Caregiver distress	16.8 (8.5)	16.8 (8.3)	16.8 (8.7)
Mini-Mental State Examination (MMSE), mean (SD)	15.7 (6.7)	17.0 (6.2)	14.4 (6.9)

	Total	Citalopram	Placebo
ADCS - Activities of Daily Living (ADL), mean (SD)	42.8 (18.4)	44.6 (19.0)	41.1 (17.8)

NBRS agitation range: 0, 18; higher scores indicate more severe symptoms

CMAI range: 14, 70; higher scores indicate more severe symptoms

NPI total frequency by severity range; 0, 144; higher scores indicate more severe symptoms

MMSE range: 0, 30; higher scores indicate better functioning

ADCS-ADL range: 0, 78; higher scores indicate better functioning

Table 2

Primary and secondary outcomes

	Citalopram	Placebo	p-value
No. randomized	94	92	
No. with any week 9 data	86	83	
Primary agitation outcomes			
Neurobehavioral Rating Scale (NBRS), agitation subscale			
Estimated score at 9 weeks*, mean (se)	4.33 (0.31)	5.26 (0.31)	
Estimated treatment effect* (citalopram - placebo), mean (95% CI)	−0.93	(−1.80, −0.06)	0.04
Clinical global impression of change in agitation (ADCS-CGIC), n (%)			
Marked improvement	12 (14%)	2 (3%)	
Moderate improvement	22 (26%)	19 (23%)	
Minimal improvement	25 (29%)	20 (25%)	
No change	17 (20%)	23 (28%)	
Minimal worsening	6 (7%)	11 (14%)	
Moderate worsening	3 (4%)	5 (6%)	
Marked worsening	1 (1%)	1 (1%)	
Estimated treatment effect† (citalopram vs placebo), odds ratio (95% CI)	2.13	(1.23, 3.69)	0.007
Secondary agitation outcomes			
Cohen Mansfield Agitation Inventory (CMAI)			
Estimated score at 9 weeks*, mean (se)	23.81 (0.62)	26.19 (0.63)	
Estimated treatment effect* (citalopram - placebo), mean (95% CI)	−2.38	(−4.13, −0.63)	0.008
Participants needing rescue lorazepam, n (%)	17 (18.9%)	20 (23.3%)	
Estimated treatment effect** (citalopram vs placebo), odds ratio (95% CI)	0.77	(0.37, 1.59)	0.48
Neuropsychiatric Inventory (NPI) - agitation subscale			
Estimated score at 9 weeks*, mean (se)	3.90 (0.35)	4.68 (0.36)	
Estimated treatment effect* (citalopram - placebo), mean (95% CI)	−0.78	(−1.77, 0.21)	0.12
Secondary efficacy outcomes			
ADCS - Activities of Daily Living (ADCS-ADL)			
Estimated score at 9 weeks*, mean (se)	40.20 (0.78)	41.31 (0.79)	

	Citalopram	Placebo	p-value
Estimated treatment effect* (citalopram - placebo), mean (95% CI)	−1.11	(−3.30, 1.08)	0.32
Neuropsychiatric Inventory (NPI) - total score			
Estimated score at 9 weeks*, mean (se)	21.20 (1.67)	27.23 (1.70)	
Estimated treatment effect* (citalopram - placebo), mean (95% CI)	−6.03	(−10.75, −1.32)	0.01
Neuropsychiatric Inventory (NPI) - caregiver distress			
Estimated score at 9 weeks*, mean (se)	9.47 (0.79)	12.17 (0.81)	
Estimated treatment effect* (citalopram - placebo), mean (95% CI)	−2.70	(−4.94, −0.47)	0.02
Secondary safety outcomes			
Mini Mental State Examination (MMSE)			
Estimated score at 9 weeks*, mean (se)	16.83 (0.32)	15.33 (0.33)	
Estimated treatment effect* (citalopram - placebo), mean (95% CI)	−1.05	(−1.97, −0.13)	0.03
Get Up and Go (GUG)			
Estimated time (seconds) at 9 weeks*, mean (se)	19.38 (0.72)	18.59 (0.74)	
Estimated treatment effect* (citalopram - placebo), mean (95% CI)	0.79	(−1.26, 2.83)	0.45

SE = standard error, CI = confidence interval.

*The score and treatment effect are the model-based estimates calculated using mixed effects regression models. The treatment effect is the difference of the scores at week 9 controlling for baseline score and MMSE. A negative number favors citalopram for NBRS, CMAI, NPI and GUG. A positive number favors citalopram for MMSE and ADCS-ADL. 90 participants in citalopram and 85 participants in placebo had at least one NBRS follow-up measurement. 86 participants in citalopram and 81 participants in placebo had NBRS data at week 9. 85 participants in citalopram and 79 participants in placebo had MMSE data at week 9. For CMAI, NPI and ADCS-ADL, 86 participants in citalopram and 83 participants in placebo had data at week 9.

**The treatment effect estimate is the odds ratio (calculated using logistic regression) of using rescue lorazepam for citalopram vs. placebo. A number less than one favors citalopram. 90 participants in citalopram and 86 participants in placebo had data on lorzaepam use for at least one follow-up visit and were included.

†The treatment effect estimate is the odds ratio (calculated using proportional odds logistic regression) of being at or better than a given ADCS-CGIC category for citalopram vs. placebo. A number greater than one favors citalopram. 86 participants in citalopram and 81 participants in placebo had data on the ADCS-CGIC at week 9.

Table 3

Patients experiencing adverse events

	Citalopram	Placebo	OR* (95% CI)	p-value
No. randomized	94	92		
No. with adverse event data**	90	86		
Death, n	0	1		
Serious adverse events†, n	8	7		
Prolonged QT interval on ECG**, n (%)	3 (12.5)	1 (4.3)		
Weight loss > 5% at week 9, n (%)	1 (1.3)	8 (10.3)		0.02
Hyponatremia, n (%)	4 (5%)	6 (8%)		0.52
Get up and Go timed assessment at week 9				
Walk time > 12 seconds, n (%)	53 (67.9)	45 (61.6)	1.32 (0.67, 2.58)	0.42
Walk time > 20 seconds, n (%)	21 (26.9)	19 (26.0)	1.05 (0.51, 2.16)	0.90
Adverse events collected via prompted questions, n (%)				
Confusion	69 (76.7)	72 (83.7)	0.64 (0.30, 1.36)	0.24
Anxiety	65 (72.2)	66 (76.7)	0.79 (0.40, 1.56)	0.49
Fatigue	54 (60.0)	53 (61.6)	0.93 (0.51, 1.71)	0.83
Gait instability	50 (55.6)	44 (51.2)	1.19 (0.66, 2.16)	0.56
Somnolence	47 (52.2)	42 (48.8)	1.15 (0.63, 2.07)	0.65
Anorexia	40 (44.4)	26 (30.2)	1.85 (0.99, 3.43)	0.05
Joint pain	40 (44.4)	48 (55.8)	0.63 (0.35, 1.15)	0.13
Rhinitis	33 (36.7)	30 (34.9)	1.08 (0.58, 2.00)	0.81
Asthenia	29 (32.2)	30 (34.9)	0.89 (0.47, 1.66)	0.71
Muscle pain	29 (32.2)	34 (39.5)	0.73 (0.39, 1.35)	0.31
Insomnia	28 (31.1)	39 (45.3)	0.54 (0.29, 1.01)	0.05
Cough	27 (30.0)	26 (30.2)	0.99 (0.52, 1.88)	0.97
Diarrhea	25 (27.8)	12 (14.0)	2.37 (1.10, 5.10)	0.03
Tremor	23 (25.6)	16 (18.6)	1.50 (0.73, 3.09)	0.27
Indigestion	23 (25.6)	18 (20.9)	1.30 (0.64, 2.62)	0.47
Dizziness	22 (24.4)	19 (22.1)	1.14 (0.57, 2.30)	0.71
Nasal congestion	22 (24.4)	22 (25.6)	0.94 (0.48, 1.86)	0.86

	Citalopram	Placebo	OR* (95% CI)	p-value
Headache	21 (23.3)	18 (20.9)	1.15 (0.56, 2.35)	0.70
Dry mouth	21 (23.3)	24 (27.9)	0.79 (0.40, 1.55)	0.49
Upper respiratory infection	17 (18.9)	9 (10.5)	1.99 (0.84, 4.75)	0.12
Falls	15 (16.7)	10 (11.6)	1.52 (0.64, 3.60)	0.34
Decreased libido	14 (15.6)	18 (20.9)	0.70 (0.32, 1.50)	0.36
Abdominal pain	14 (15.6)	19 (22.1)	0.65 (0.30, 1.40)	0.27
Constipation	13 (14.4)	22 (25.6)	0.49 (0.23, 1.05)	0.07
Visual disturbance	12 (13.3)	14 (16.3)	0.79 (0.34, 1.82)	0.58
Yawning	11 (12.2)	17 (19.8)	0.57 (0.25, 1.29)	0.17
Sweating	9 (10.0)	12 (14.0)	0.69 (0.27, 1.72)	0.42
Fever	9 (10.0)	2 (2.3)		0.03
Sore throat	7 (7.8)	7 (8.1)	0.95 (0.32, 2.84)	0.93
Suicidal thoughts	6 (6.7)	4 (4.7)		0.21
Ejaculatory dysfunction**	6 (12.5)	3 (6.3)		0.16
Nausea	5 (5.6)	6 (7.0)	0.78 (0.23, 2.67)	0.70
Vomiting	5 (5.6)	0		0.12
Drug allergy	4 (4.4)	4 (4.7)		0.28
Bronchitis	3 (3.3)	2 (2.3)		1.00
Pneumonia	1 (1.1)	0		1.00
Adverse events collected via open-ended questions, n (%)				
Related to pain	6 (6.8)	4 (4.7)		
Related to increased urinary frequency	4 (4.5)	2 (2.4)		
Related to balance problems	3 (3.4)	0		
Other, not related to urinary frequency, balance or pain	19	13		

*Odds ratios (OR) and p-values calculated using logistic regression or Fisher's exact (for small cell counts). A patient was counted as having the event if he/she reported the symptom during any follow-up visit.

**10 randomized patients had no data on adverse events during follow-up. ECG monitoring began in 11Nov2011; data are available for 48 participants (24 in citalopram and 24 in placebo). 96 men have data on ejaculatory dysfunction. 84 patients in citalopram and 78 patients in placebo had electrolyte data for sodium measurements.

†For details on serious adverse events, see Supplementary Table 1.