Original Investigation

Effect of Citalopram on Agitation in Alzheimer Disease
The CitAD Randomized Clinical Trial

Anton P. Porsteinsson, MD; Lea T. Drye, PhD; Bruce G. Pollock, MD, PhD; D. P. Devanand, MD; Constantine Frangakis, PhD; Zahinoor Ismail, MD; Christopher Marano, MD; Curtis L. Meinert, PhD; Jacobo E. Mintzer, MD, MBA; Cynthia A. Munro, PhD; Gregory Pelton, MD; Peter V. Rabins, MD; Paul B. Rosenberg, MD; Lon S. Schneider, MD; David M. Shade, JD; Daniel Weintraub, MD; Jerome Yesavage, MD; Constantine G. Lyketsos, MD, MHS; for the CitAD Research Group

IMPORTANCE Agitation is common, persistent, and associated with adverse consequences for patients with Alzheimer disease. Pharmacological treatment options, including antipsychotics are not satisfactory.

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

DESIGN, SETTING, AND PARTICIPANTS The Citalopram for Agitation in Alzheimer Disease Study (CitAD) was a randomized, placebo-controlled, double-blind, parallel group trial that enrolled 186 patients with probable Alzheimer disease and clinically significant agitation from 8 academic centers in the United States 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. Dosage began at 10 mg per day with planned titration to 30 mg per day over 3 weeks based on response and tolerability.

MAIN OUTCOMES AND MEASURES Primary outcome measures were based on scores from the 18-point Neurobehavioral Rating Scale agitation subscale (NBRS-A) and the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC). Other outcomes were based on scores from the Cohen-Mansfield Agitation Inventory (CMAI) and the Neuropsychiatric Inventory (NPI), ability to complete activities of daily living (ADLs), caregiver distress, cognitive safety (based on scores from the 30-point Mini Mental State Examination [MMSE]), and adverse events.

RESULTS Participants who received citalopram showed significant improvement compared with those who received placebo on both primary outcome measures. The NBRS-A estimated treatment difference at week 9 (citalopram minus placebo) was −0.93 (95% CI, −1.80 to −0.06), $P = .04$. Results from the mADCS-CGIC showed 40% of citalopram participants having moderate or marked improvement from baseline compared with 26% of placebo recipients, with estimated treatment effect (odds ratio [OR] of being at or better than a given CGIC category) of 2.13 (95% CI, 1.23-3.69), $P = .01$. Participants who received 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; $P = .03$) and QT interval prolongation (18.1 ms; 95% CI, 6.1-30.1; $P = .01$) were seen in the citalopram group.

CONCLUSIONS AND RELEVANCE Among patients with probable Alzheimer disease and agitation who were receiving psychosocial intervention, the addition of citalopram compared with placebo significantly reduced agitation and caregiver distress; however, cognitive and cardiac adverse effects of citalopram may limit its practical application at the dosage of 30 mg per day.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The CitAD Research Group members are listed at the end of this article.

Corresponding Author: Anton P. Porsteinsson, MD, Department of Psychiatry, University of Rochester School of Medicine and Dentistry, 435 E Henrietta Rd, Rochester, NY 14620 (anton_porsteinsson@urmc.rochester.edu).

Neuropsychiatric symptoms occur in a majority of patients with Alzheimer disease. 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. Antipsychotic drugs 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) frequently used in older individuals,[11,12] 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 2 randomized, masked, follow-up studies, Pollock and colleagues[17-19] 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 Alzheimer disease population.

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

Methods

Study Design and Oversight

The CitAD study was an investigator-initiated multicenter, randomized, placebo-controlled, double-blind, parallel group trial that enrolled patients from 8 US and Canadian academic centers. 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. The study protocol and amendments were approved by the institutional review board (IRB) or research ethics board 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 provide 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 and Eligibility Criteria

CitAD participants had probable Alzheimer disease, as determined by National Institute of Neurological and Communication Disorders and Stroke-Alzheimer Disease and Related Disorders Association[21] criteria, with Mini-Mental State Examination (MMSE)[22] scores from 5 to 28 being inclusive, and had clinically significant agitation, for which a physician determined that medication was appropriate (based on ratings of [1] occurring very frequently, or [2] occurring frequently with moderate or marked severity on the agitation/aggression domain [a 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 per week with the patient was required to supervise medication use and participate in outcomes assessments. Medications for the treatment of Alzheimer disease (cholinesterase inhibitors and memantine) at stable doses within the month preceding randomization were allowed. Withdrawal of psychotropic medications other than predefined rescue medications was required. Adequate previous treatment or contraindication to citalopram was exclusionary. Prolonged QT interval on an electrocardiogram was later added as an exclusion criterion (see Interventions). Race and ethnicity were self-reported based on categories defined by the National Institutes of Health.

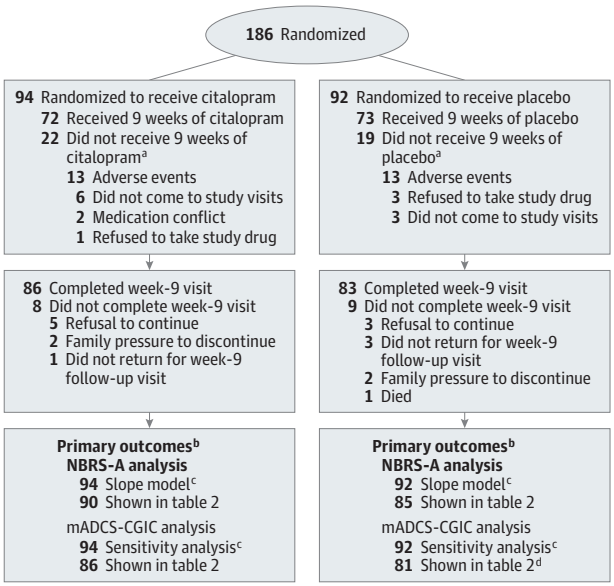
Interventions

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 per 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 US 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 greater than 450 ms for men and greater than 475 ms 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.

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 3 components: provision of educational materials; 24-hour availability for crisis management; and a 20- to 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 communicate feelings, counseling regarding specific caregiv-

Figure 1. Participant Flow in Randomization to Citalopram vs Placebo for Agitation in Alzheimer Disease



Data for the individuals who were initially screened for eligibility, those excluded, and the reasons for exclusion were not available.

[a] Data from participants were included in the analysis in the originally assigned treatment group, regardless of treatment adherence.

[b] Comparisons comprising the primary outcomes: (1) difference in week-9 scores between citalopram and placebo on the Neurobehavioral Rating Scale-agitation subscale (NBRS-A) calculated using mixed-effects regression; and (2) ratings on the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC) at week 9 calculated using proportional odds regression.

[c] NBRS slope model included data from all randomized participants. For the mADCS-CGIC sensitivity analyses, outcomes were multiply imputed.

[d] Two participants in the placebo group underwent the week-9 visit but the mADCS-CGIC was not administered.

ing 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 based on scores from the agitation subscale of the Neurobehavioral Rating Scale (NBRS-A)[25] (range, 0-18 with higher scores indicating more severe symptoms) and the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC)[26] (range, 1-7 with 1 indicating marked improvement and 7 indicating 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 Alzheimer disease, producing a global rating of change in agitation and a measure of clinical significance.

Secondary efficacy outcomes were based on scores from the Neuropsychiatric Inventory (NPI)[23] (frequency by severity range, 0-144 with higher scores indicating more severe symptoms), individual NPI domain ratings, NPI caregiver distress ratings (range, 0-60 with higher scores indicating more severe distress), the Cohen-Mansfield Agitation Inventory (CMAI)[27] (range, 14-70 with higher scores indicating more severe symptoms), the Alzheimer Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)[28] (range, 0-78 with higher scores indicating better functioning), and cumulative lorazepam dose. Important secondary safety outcomes included MMSE,[22] a measure of cognitive abilities (range, 0-30 with higher scores indicating better functioning); 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.

Sensitivity analyses for the NBRS-A outcome were performed using the 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 (reported as *marked worsening-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] Sensitivity analyses for the mADCS-CGIC outcome were performed by using multiple imputation to estimate missing week 9 data.

The proportion of participants experiencing adverse events was compared between treatment groups using the Fisher 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 an accounting of pills from returned medication bottles using the Wilcoxon rank-sum test.

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc) and R version 2.13.1 (R Foundation for Statistical Computing, http://www.R-project.org). All *P* values were 2-sided and *P* value of less than .05 was the threshold for statistical significance. No adjustments were made for multiple comparisons.

A detailed description of the power calculations was published previously.[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 with placebo. For the mADCS-CGIC proportional odds analysis, the study was designed to have power greater than 80% to detect a difference

Table 1. Patient Characteristics at Baseline

	Total (N=186)	Citalopram (n=94)	Placebo (n=92)
Age, mean (SD), y	78 (8)	78 (9)	79 (8)
Women, No. (%)	85 (46)	44 (47)	41 (45)
Race/ethnicity, No. (%)			
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, No. (%)			
No high school diploma	52 (28)	25 (27)	27 (29)
High school diploma	43 (23)	20 (21)	23 (25)
Associates degree or some college	29 (16)	18 (19)	11 (12)
Bachelor's degree	37 (20)	21 (22)	16 (17)
Professional or graduate degree	25 (13)	10 (11)	15 (16)
Duration of dementia, mean (SD), y	5 (4)	5 (4)	5 (4)
Concomitant medications, No. (%)			
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, No. (%)[a]	25 (13)	11 (12)	14 (15)
Assessment, mean (SD), score			
NBRS-A[b]	7.6 (3.1)	7.4 (3.3)	7.8 (3.0)
CMAI[c]	28.2 (6.7)	27.7 (6.7)	28.7 (6.7)
NPI[d]			
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)
MMSE[e]	15.7 (6.7)	17.0 (6.2)	14.4 (6.9)
ADCS-ADL[f]	42.8 (18.4)	44.6 (19.0)	41.1 (17.8)

Abbreviations: ADCS-ADL, Alzheimer Disease Cooperative Study-activities of daily living; CMAI, Cohen-Mansfield Agitation Inventory; MMSE, Mini Mental State Examination; NBRS-A, Neurobehavioral Rating Scale-agitation subscale; NPI, Neuropsychiatric Inventory.

[a] Indicates history before Alzheimer disease.

[b] NBRS-A range, 0 to 18 (higher scores indicate more severe symptoms).

[c] CMAI range, 14 to 70 (higher scores indicate more severe symptoms).

[d] NPI total frequency by severity range, 0 to 144 (higher scores indicate more severe symptoms; 2 of the 12 NPI domains are shown [0-12 range for each]).

[e] MMSE range, 0 to 30 (higher scores indicate better functioning).

[f] ADCS-ADL range, 0 to 78 (higher scores indicate better functioning).

of 20% between citalopram and placebo in the proportions of patients who improved (or worsened).

Results

Patients

The study enrolled 186 participants between August 2009 and January 2013 (94 were assigned to receive citalopram and 92 to placebo). Although intent of the study was to enroll 200 participants per protocol by December 31, 2012, recruitment slowed notably toward the end of this timeframe. **Figure 1** summarizes patient recruitment, participation, and attrition. Baseline characteristics between study groups were similar (**Table 1**), except participants assigned to receive placebo had lower mean MMSE scores. On average, participants were 78 or 79 years of age, 46% were women, 65% were white and non-Hispanic, 89% were community dwelling, and all were 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 receiving citalopram showed significant improvement compared with placebo on both primary outcome measures (**Table 2**). At week 9, the raw NBRS-A scores (unadjusted mean [SD]) for the citalopram group were 4.1 (3.0) and for the placebo group were 5.4 (3.2) (crude difference, 1.3; 95% CI, 2.6-3.5; $P = .01$) (**Figure 2**). The mixed-model estimated difference in week 9 NBRS-A scores for citalopram vs placebo was −0.93 (95% CI, −1.80 to −0.06; $P = .04$) with negative numbers favoring citalopram. The model estimated differences in scores at the 2 interim visits were −0.58 (95% CI, −1.44 to 0.29; $P = .19$) at week 3 and −1.12 (95% CI, −1.98 to −0.26; $P = .01$) at week 6. The estimated difference in linear slopes over all study visits was −0.12 (95% CI, −0.22 to −0.02; $P = .02$). Results for the NBRS-A were virtually identical for the GEE model. The GEE estimated difference in week-9 scores was −0.94 (95% CI, −1.80 to −0.07; $P = .03$).

Table 2. Primary and Secondary Outcomes[a]

	Citalopram		Placebo	*P* Value
No. randomized	94		92	
No. with any week-9 data	86		83	
Primary Agitation Outcomes				
NBRS-A[b]				
No. with ≥1 follow-up measurement	90		85	
No. with week-9 data	86		81	
Estimated score at 9 weeks, mean (SE)	4.33 (0.31)		5.26 (0.31)	
Estimated treatment effect, mean (95% CI)		−0.93 (−1.80 to −0.06)[c]		.04
ADCS-CGIC, No. (%)				
No. with week-9 data	86		81	
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, OR (95% CI)[d]		2.13 (1.23 to 3.69)[e]		.007
Secondary Agitation Outcomes				
CMAI[b]				
No. with week-9 data	86		83	
Estimated score at 9 weeks, mean (SE)	23.81 (0.62)		26.19 (0.63)	
Estimated treatment effect, mean (95% CI)		−2.38 (−4.13 to −0.63)[c]		.008
Participants needing rescue lorazepam, No. (%)[f]	17 (18.9)		20 (23.3)	
No. with ≥1 follow-up visit	90		86	
Estimated treatment effect, OR (95% CI)[c]		0.77 (0.37 to 1.59)[g]		.48
NPI-agitation subscale[b]				
Estimated score at 9 weeks, mean (SE)	3.90 (0.35)		4.68 (0.36)	
Estimated treatment effect, mean (95% CI)		−0.78 (−1.77 to 0.21)[c]		.12
Secondary Efficacy Outcomes				
ADCS-ADL[b]				
No. with week-9 data	86		83	
Estimated score at 9 weeks, mean (SE)	40.20 (0.78)		41.31 (0.79)	
Estimated treatment effect, mean (95% CI)		−1.11 (−3.30 to 1.08)[h]		.32
NPI-total score[b]				
No. with week-9 data[i]	86		83	
Estimated score at 9 weeks, mean (SE)	21.20 (1.67)		27.23 (1.70)	
Estimated treatment effect, mean (95% CI)		−6.03 (−10.75 to −1.32)[c]		.01
NPI caregiver distress subscore[b]				
Estimated score at 9 weeks, mean (SE)	9.47 (0.79)		12.17 (0.81)	
Estimated treatment effect, mean (95% CI)		−2.70 (−4.94 to −0.47)[c]		.02
Secondary Safety Outcomes				
MMSE[b]				
No. with week-9 data	85		79	
Estimated score at 9 weeks, mean (SE)	16.83 (0.32)		15.33 (0.33)	
Estimated treatment effect, mean (95% CI)		−1.05 (−1.97 to −0.13)[h]		.03
GUG[b]				
No. with week-9 data	84		79	
Estimated time (seconds) at 9 weeks, mean (SE)	19.38 (0.72)		18.59 (0.74)	
Estimated treatment effect, mean (95% CI)		0.79 (−1.26 to 2.83)[c]		.45

Abbrevation: ADCS, Alzheimer Disease Cooperative Study; ADL, activities of daily living; CGIC, clinical global impression of change in agitation; CMAI, Cohen Mansfield Agitation Inventory; GUG, Get Up and Go; MMSE Mini Mental State Examination; NBRS-A, Neurobehavioral Rating Scale-agitation subscale; NPI, Neuropsychiatric Inventory; OR, odds ratio.

[a] All estimated treatment effects compare citalopram vs placebo.

[b] The score and treatment effect are model-based estimates calculated using mixed-effects regression models. The treatment effect is the difference in scores at week 9, controlling for baseline score and MMSE.

[c] A negative treatment effect value favors citalopram for NBRS, CMAI, NPI and GUG.

[d] The treatment effect estimate is the OR (calculated using proportional odds logistic regression) of being at or better than a given ADCS-CGIC category for citalopram vs placebo.

[e] A treatment effect value greater than 1 favors citalopram.

[f] The treatment effect estimate is the OR (calculated using logistic regression) of using rescue lorazepam for citalopram vs placebo.

[g] A number less than 1 favors citalopram.

[h] A positive treatment effect value favors citalopram for MMSE and ADCS-ADL.

[i] Same values apply for the NPI-agitation subscale and the NPI caregiver distress subscale.

Modified ADCS-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 [OR] of being at or better than a given CGIC category) of 2.13 (95% CI, 1.23-3.69; P = .007). The estimated OR for the sensitivity analysis including imputed values for missing data was 2.10 (95% CI,1.21-3.64).

Secondary Outcomes

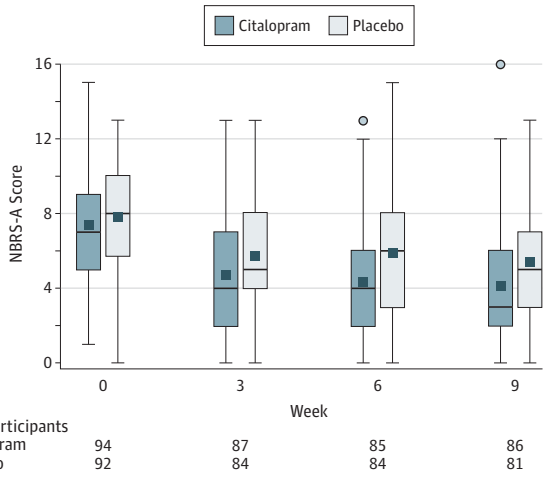
Relative to placebo, citalopram was associated with improved scores on the CMAI with an estimated difference in week-9 scores of −2.38 (95% CI, −4.13 to −0.63; P = .008). On the NPI total score, estimated differences for citalopram over placebo in week 9 scores were -6.03 (95% CI, −10.75 to −1.32; P = .01), on the NPI agitation subscale, −0.78 (95% CI, −1.77 to 0.21; P = .12), and on the NPI caregiver distress, −2.70 (95% CI, −4.94 to −0.47; P = .02). There was no significant difference between groups on the ADCS-ADL scale. There was no difference between the 2 treatment groups in the use of rescue lorazepam (Table 2).

Safety and Adherence

There was no difference in adherence between the 2 study groups. MMSE results showed greater cognitive worsening with citalopram (−1.05 points; 95% CI, −1.97 to −0.13; P = .03) (Table 2). Anorexia, diarrhea, and fever were more common among participants in the citalopram group and weight loss and insomnia among participants in the placebo group (**Table 3**). Falls were more frequent in the citalopram group and remained so even after controlling for baseline differences. An increase in upper respiratory tract infections was also noted in the citalopram group. The citalopram group may have shown a slight increase in gait impairment as measured by the Get Up and Go, but the rate of hyponatremia did not differ appreciably between the groups. Frequency of serious adverse events was comparable between treatment groups (eTable in the Supplement). There was 1 death in the placebo group.

Electrocardiogram (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 = .004), and more participants in the citalopram group showed a QTc increase of greater than 30 ms from enrollment to week 3 than participants in the placebo group (7 vs 1; Fisher exact P = .05). Four participants (3 citalopram and 1 placebo) showed QTc prolongation (>450 ms for men and >475 ms for women).

Figure 2. Neurobehavioral Rating Scale (NBRS)-Agitation Subscale



Higher NBRS scores indicate more severe symptoms. The horizontal bar inside the boxes indicates the median, the square in the boxes indicates the mean, and the lower and upper ends of the boxes are the first and third quartiles. The whiskers indicate values within 1.5 × the interquartile range from the upper or lower quartile (or the minimum and maximum if within 1.5 × the interquartile range of the quartiles) and data more extreme than the whiskers are plotted individually as outliers.

Discussion

Citalopram treatment led to a reduction in agitation in patients with Alzheimer disease. 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 in the placebo group. 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 raised concern about the 30 mg per day dose used in this study and may limit the clinical utility of the findings.

Safe and effective treatments for agitation remain elusive and options are limited. Patients in this trial had substantial, disruptive behavioral symptoms at the same level or greater than patients with Alzheimer disease who received antipsychotic drugs in the CATIE-AD (Clinical Antipsychotic Trial of Intervention Effectiveness study for Alzheimer's Disease) 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 with that of antipsychotic drugs 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 per day of citalopram improved agitation. Similar to previous studies, a robust rating scales response was observed in the placebo group.[6]

The MMSE was used 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 among patients in the placebo group but worsened among those in the citalopram group, 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 antipsychotic drugs in similarly designed trials[6] but lower than the

Table 3. Patients Experiencing Adverse Events

	Citalopram	Placebo	OR (95% CI)[a]	*P* Value[a]
No. randomized	94	92		
No. with adverse event data[b]	90	86		
No. who died	0	1		
Serious adverse events, No.[c]	8	7		
Prolonged QT interval on ECG, No. (%)[d]	3 (12.5)	1 (4.3)		
Weight loss >5% at week 9, No. (%)	1 (1.3)	8 (10.3)		.02
Hyponatremia, No. (%)[e]	4 (5)	6 (8)		.52
Get up and Go timed assessment at week 9, No. (%)				
Walk time >12 s	53 (67.9)	45 (61.6)	1.32 (0.67-2.58)	.42
Walk time >20 s	21 (26.9)	19 (26.0)	1.05 (0.51-2.16)	.90
Adverse events collected via prompted questions, No. (%)				
Confusion	69 (76.7)	72 (83.7)	0.64 (0.30-1.36)	.24
Anxiety	65 (72.2)	66 (76.7)	0.79 (0.40-1.56)	.49
Fatigue	54 (60.0)	53 (61.6)	0.93 (0.51-1.71)	.83
Gait instability	50 (55.6)	44 (51.2)	1.19 (0.66-2.16)	.56
Somnolence	47 (52.2)	42 (48.8)	1.15 (0.63-2.07)	.65
Anorexia	40 (44.4)	26 (30.2)	1.85 (0.99-3.43)	.05
Joint pain	40 (44.4)	48 (55.8)	0.63 (0.35-1.15)	.13
Rhinitis	33 (36.7)	30 (34.9)	1.08 (0.58-2.00)	.81
Asthenia	29 (32.2)	30 (34.9)	0.89 (0.47-1.66)	.71
Muscle pain	29 (32.2)	34 (39.5)	0.73 (0.39-1.35)	.31
Insomnia	28 (31.1)	39 (45.3)	0.54 (0.29-1.01)	.05
Cough	27 (30.0)	26 (30.2)	0.99 (0.52-1.88)	.97
Diarrhea	25 (27.8)	12 (14.0)	2.37 (1.10-5.10)	.03
Tremor	23 (25.6)	16 (18.6)	1.50 (0.73-3.09)	.27
Indigestion	23 (25.6)	18 (20.9)	1.30 (0.64-2.62)	.47
Dizziness	22 (24.4)	19 (22.1)	1.14 (0.57-2.30)	.71
Nasal congestion	22 (24.4)	22 (25.6)	0.94 (0.48-1.86)	0.86
Headache	21 (23.3)	18 (20.9)	1.15 (0.56-2.35)	.70
Dry mouth	21 (23.3)	24 (27.9)	0.79 (0.40-1.55)	.49
Upper respiratory tract infection	17 (18.9)	9 (10.5)	1.99 (0.84-4.75)	.12
Falls	15 (16.7)	10 (11.6)	1.52 (0.64-3.60)	.34
Decreased libido	14 (15.6)	18 (20.9)	0.70 (0.32-1.50)	.36
Abdominal pain	14 (15.6)	19 (22.1)	0.65 (0.30-1.40)	.27
Constipation	13 (14.4)	22 (25.6)	0.49 (0.23-1.05)	.07
Visual disturbance	12 (13.3)	14 (16.3)	0.79 (0.34-1.82)	.58
Yawning	11 (12.2)	17 (19.8)	0.57 (0.25-1.29)	.17
Sweating	9 (10.0)	12 (14.0)	0.69 (0.27-1.72)	.42
Fever	9 (10.0)	2 (2.3)		.03
Sore throat	7 (7.8)	7 (8.1)	0.95 (0.32-2.84)	.93
Suicidal thoughts	6 (6.7)	4 (4.7)		.21
Ejaculatory dysfunction[f]	6 (12.5)	3 (6.3)		.16
Nausea	5 (5.6)	6 (7.0)	0.78 (0.23-2.67)	.70
Vomiting	5 (5.6)	0		.12
Drug allergy	4 (4.4)	4 (4.7)		.28
Bronchitis	3 (3.3)	2 (2.3)		>.99
Pneumonia	1 (1.1)	0		>.99
Adverse events collected via open-ended questions, No. (%)				
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		

Abbreviation: OR, odds ratio.

[a] ORs and *P* values were calculated using logistic regression or Fisher exact tests (for small cell counts). A patient was counted as having an event if the symptom was reported during any follow-up visit.

[b] Ten randomized patients had no data on adverse events during follow-up.

[c] For details on serious adverse events, see eTable in Supplement.

[d] ECG monitoring began November 11, 2011; data are available for 48 participants (24 in the citalopram group and 24 in the placebo group).

[e] Eighty-four patients in the citalopram group and 78 patients in the placebo group had electrolyte data for sodium measurements.

[f] Ninety-six men had data on ejaculatory dysfunction.

minimum clinically significant change of 1.4 points, considered by many experts.[34] This finding is consistent with another study that reported declines in verbal learning and psychomotor speed in patients receiving citalopram,[35] and with prior epidemiological data.[36] Conversely, citalopram at 20 mg per day 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 disease.[37] Therefore, although citalopram had a small negative effect 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 affects the course of Alzheimer disease.

The QT interval prolongation observed in this study is consistent with the US Food and Drug Administration (FDA) advisory[24] and citalopram's current prescribing information. This study maintained a 30 mg per day target dose of citalopram after the FDA advisory and the findings suggest that 30 mg per day in patients with Alzheimer disease should generally be avoided. Current prescribing information recommends a maximum daily dose of 20 mg of citalopram for patients older than 60 years of age because of substantially higher exposures, decreased clearance, and prolonged cardiac repolarization potential.[38] This trial did not have enough patients treated with the dose 20 mg per day to assess efficacy at that level.

Strengths of the study include the following: (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 Alzheimer disease patients; (6) semistructured psychosocial intervention administered to all patients and caregivers; (7) consistent results across sites supporting generalizability; and (8) consistent findings across multiple measures of agitation and analysis methods.

Limitations of the study include the following: (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 effect of citalopram on agitation in non-Alzheimer disease forms of dementia; (4) unknown effect of 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; and (8) lack of data collection on potential patients who declined to participate or failed screening.

Conclusions

Identifying drugs outside the antipsychotic class with targeted antiagitation effects that provide greater benefit or lower risk among patients with Alzheimer disease is a research priority. Although citalopram at 30 mg daily was associated with clinically meaningful reduction in agitation in patients with Alzheimer disease over 9 weeks of treatment comparable to what is seen with use of antipsychotic drugs, citalopram showed mild cognitive and concerning cardiac adverse effects and cannot be generally recommended as an alternative treatment option at that dose. Additionally, there are insufficient data 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.

ARTICLE INFORMATION

Author Affiliations: University of Rochester School of Medicine and Dentistry, Rochester, New York (Porsteinsson); Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Drye, Frangakis, Meinert, Shade); Campbell Institute, CAMH, University of Toronto, Toronto, Ontario, Canada (Pollock); Division of Geriatric Psychiatry, New York State Psychiatric Institute, New York (Devanand, Pelton); College of Physicians and Surgeons of Columbia University, New York, New York (Devanand); Departments of Psychiatry and Neurology, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada (Ismail); Johns Hopkins Bayview and Johns Hopkins School of Medicine, Baltimore, Maryland (Marano, Munro, Rabins, Rosenberg, Lyketsos); Clinical Biotechnology Research Institute, Roper St Francis Healthcare, Charleston, South Carolina (Mintzer); University of Southern California Keck School of Medicine, Los Angeles (Schneider); Perelman School of Medicine at the University of Pennsylvania, Philadelphia (Weintraub); Stanford University School of Medicine, Stanford, California (Yesavage); VA Palo Alto Health Care System, Stanford, California (Yesavage).

Author Contributions: Dr Porsteinsson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Porsteinsson, Drye, Pollock, Devanand, Frangakis, Meinert, Mintzer, Munro, Rabins, Rosenberg, Schneider, Shade, Weintraub, Yesavage, Lyketsos.
Acquisition of data: Porsteinsson, Pollock, Devanand, Ismail, Marano, Mintzer, Pelton, Rosenberg, Schneider, Weintraub, Yesavage.
Analysis and interpretation of data: Porsteinsson, Drye, Pollock, Devanand, Frangakis, Ismail, Marano, Meinert, Mintzer, Munro, Pelton, Rabins, Rosenberg, Schneider, Shade, Weintraub, Lyketsos.
Drafting of the manuscript: Porsteinsson, Drye, Frangakis, Schneider, Shade, Lyketsos.
Critical revision of the manuscript for important intellectual content: Porsteinsson, Drye, Pollock, Devanand, Frangakis, Ismail, Marano, Meinert, Mintzer, Munro, Pelton, Rabins, Rosenberg, Schneider, Shade, Weintraub, Yesavage, Lyketsos.
Statistical analysis: Drye, Frangakis, Meinert, Shade.
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Study supervision: Porsteinsson, Drye, Pollock, Devanand, Frangakis, Meinert, Mintzer, Rosenberg, Pelton, Schneider, Shade, Weintraub, Yesavage, Lyketsos.

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Steering Committee Voting Members: Responsibilities: study design and conduct. Resource center representatives: Constantine Lyketsos, MD, MHS (chair); Dave Shade, JD (vice chair). Clinical center directors: D. P. Devanand, MD; Jacobo Mintzer, MD, MBA; Paul Rosenberg, MD; Bruce G. Pollock, MD, PhD; Anton P. Porsteinsson, MD; Lon S. Schneider, MD; Jerome Yesavage, MD; Daniel Weintraub, MD.

Research Group Resource Centers: Responsibility: study administration. Chair's office, Johns Hopkins Bayview and Johns Hopkins School of Medicine, Baltimore, MD: Constantine Lyketsos, MD, MHS (chair); Allison Carlson, MA (lead coordinator); Dimitri Avramopoulos, MD, PhD (study geneticist); Cynthia Munro, PhD (study neuropsychologist); Peter Rabins, MD, MPH (conflict of interest officer). Coordinating center, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD: Dave Shade, JD (director); Anne Shanklin Casper, MA, CCRP (lead coordinator); Lea Drye, PhD; Constantine Frangakis, PhD; Gabrielle Jenkins, BS; Curtis Meinert, PhD; Hao-Min Pan, BA; Susan Tonascia, ScM; Ozlem Topaloglu, PhD; Matthew Toepfner, BA; Vijay Vaidya, MSc, MPH. Project Office, NIA, Bethesda, MD: Laurie Ryan, PhD (project officer).

Clinical Centers: Responsibility: data collection. Johns Hopkins Bayview and Johns Hopkins School of Medicine, Baltimore, MD: Paul Rosenberg, MD (director); Julia Pedroso, RN, MA (lead coordinator); Alyssa Bergey, MA; Allison Carlson, MA; Carol Gogel, RN; Christopher Marano, MD; Jane Pollutra, RN; Martin Steinberg, MD. Division of Geriatric Psychiatry, New York State Psychiatric Institute and Columbia University Medical Center, New York, NY: D.P. Devanand, MD (director); Corazon de la Pena (lead coordinator); Gregory H. Pelton, MD. Medical University of South Carolina, Charleston, SC: Jacobo Mintzer, MD, MBA (director); Nicholas Gregory (lead coordinator); Olga Brawman-Mintzer, MD; Allison Moroni, MA; Amanda Watts, BS; Marilyn Stuckey, RN; Courtney O'Neill, MHA. Perelman School of Medicine at the University of Pennsylvania, Philadelphia: Daniel Weintraub, MD (director); Jamie Czerniakowski, BA (lead coordinator); Suzanne DiFilippo, RN; Eugenia Mamikonyan, MS; Joel Streim, MD. University of Rochester School of Medicine, Rochester, NY: Anton P. Porsteinsson, MD (director); Bonnie Goldstein, MS, NP (coordinator); Susan Salem-Spencer, RN, MSN (coordinator); Nancy Kowalski, MS, RNC; Kimberly S. Martin, RN; Jeanne LaFountain, RN; Kelly Makino, BS; Kelly Stear, MS, NCC; Andrew Porter, BA; Asa Widman, BA. Stanford University School of Medicine, Stanford, CA: Jerome Yesavage, MD (director); Jeff Newell, BA (lead coordinator); Wes Ashford, MD; Karen Bratcher, RN; Steven Chao, MD; Jennifer Kaci Fairchild, PhD; Leah Friedman, PhD; Gerald Georgette, RN; Emily Gere, AA; Ellen Kim; Vyjeyanthi Periyakoil, MD; Arthur Traum, MD; Alda Vicencio, RN; Deryl Wicks, BA. University of Toronto, Toronto, ON, Canada: Bruce G. Pollock, MD, PhD, FRCPC (director); Dielle Miranda, MA (lead coordinator); Robert Bies, PhD; Amer Burhan, MD; Phil Gerretsen, MD; Zahinoor Ismail, MD; Benoit H. Mulsant, MD, MS; Minh-Quan Nguyen, HBsc; Tarek Rajji, MD; David Tang-Wai MD. University of Southern California Keck School of Medicine, Los Angeles: Lon S. Schneider, MD (director); Mauricio Becerra, MD (lead coordinator); Karen Dagerman, MS; Sonia Pawluczyk, MD; Bryan Spann, DO, PhD; Liberty Teodoro, RN.

Data Safety and Monitoring Board Members: Responsibility: review of accumulating data on safety and efficacy. Voting members: Kristine Yaffe, MD (chair); Stephan Arndt, PhD; Jeffrey Cummings, MD. Nonvoting members: Lea Drye, PhD; Kostas Lyketsos, MD; Laurie Ryan, MD; Dave Shade, JD.

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