Effects of Citalopram on Neuropsychiatric Symptoms in Alzheimer's Dementia: Evidence From the CitAD Study

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Objective: Citalopram has been shown to improve agitation in patients with Alzheimer's disease. The authors evaluated whether other neuropsychiatric symptoms improve with citalopram treatment compared with placebo.

Method: In this planned secondary analysis of the Citalopram for Agitation in Alzheimer's Disease study, the authors evaluated the effect of citalopram on the 12 neuropsychiatric symptom domains assessed by the Neuropsychiatric Inventory (NPI). They compared caregiver-reported NPI scores at week 9 in patients receiving citalopram (30 mg/day) or placebo with regard to both the presence or absence of individual neuropsychiatric symptoms and individual domain scores (reflecting severity) in participants who had symptoms at week 9.

Results: At week 9, participants treated with citalopram were significantly less likely to be reported as showing delusions (odds ratio=0.40), anxiety (odds ratio=0.43), and irritability/lability (odds ratio=0.38). A comparison of median scores of participants with symptoms present at week 9 showed significant differences favoring citalopram for hallucinations and favoring placebo for sleep/nighttime behavior disorders.

Conclusions: While dosage constraints must be considered because of citalopram's adverse effect profile, this agent's overall therapeutic effects in patients with Alzheimer's disease and agitation, in addition to efficacy for agitation/aggression, included reductions in the frequency of irritability, anxiety, and delusions; among patients who had these symptoms at week 9, they included a reduction in the severity of hallucinations but an increase in the severity of sleep/nighttime behavior disorders.

AJP in Advance (doi: 10.1176/appi.ajp.2016.15020248)

Alzheimer's disease affects more than 5 million people in the United States (1), and its prevalence is increasing. Neuropsychiatric symptoms accompany cognitive decline in the vast majority of cases; estimates of the prevalences of these symptoms range from 61% to 75% in older adults with dementia and 31% to 51% in those with mild cognitive impairment (2, 3). The presence of neuropsychiatric symptoms is associated with more rapid disease progression, worse patient outcomes, excess morbidity and mortality, greater use of health care services, earlier nursing home placement, and increased caregiver burden (4, 5).

Nonpharmacological strategies are recommended as first-line treatment for neuropsychiatric symptoms (6). These interventions appear less effective for more severe symptoms, and in clinical settings they are implemented much less frequently than pharmacological interventions (7). No pharmacotherapy has been approved for this indication by the Food and Drug Administration. Atypical antipsychotics, which have the best-established albeit limited efficacy, are the most frequently used agents in practice (8–10). This is problematic, as growing evidence suggests serious safety concerns, increased mortality, and uncertain efficacy when using antipsychotics in patients with dementia (11–14). A hypothesized cause of agitation in Alzheimer's disease is disease-associated neurodegeneration that gradually disrupts, then destroys, the brain monoamine system, including ascending serotonergic pathways, leading to an imbalance in the serotonergic-dopaminergic axis (15).

Citalopram, a selective serotonin reuptake inhibitor (SSRI) frequently used in older individuals (16), has been proposed as an alternative to antipsychotics in the treatment of neuropsychiatric symptoms in dementia (17, 18). Building on earlier preliminary data, the Citalopram for Agitation in Alzheimer's Disease (CitAD) study investigated the efficacy and safety of citalopram in patients with Alzheimer's disease and agitation (19). In the primary analysis of CitAD data (20), the estimated treatment difference at week 9 (citalopram minus placebo) based on the agitation subscale of the Neurobehavioral Rating Scale (21) was −0.93 points (95% CI=−1.80, −0.06, p=0.04). Forty percent of the citalopram

group were rated as moderately or markedly improved on the modified Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (CGIC) (22), compared with 26% of the placebo group, with an estimated treatment effect (the odds ratio of being at or better than a given CGIC category) of 2.13 (95% CI=1.23, 3.69, p=0.01). The citalopram-treated group also showed significant improvement on the short-form Cohen-Mansfield Agitation Inventory (23), the Neuropsychiatric Inventory (NPI) (24), and caregiver distress ratings, but not on the NPI agitation subscale, the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (25), or in less use of lorazepam (20). Worsening of cognition (as measured by the Mini-Mental State Examination) and QT interval prolongation were seen in the citalopram group (20). On the NPI's agitation domain, the effect of citalopram was no better than that of placebo; thus, the significant improvements seen on the full NPI were most likely related to improvements in other neuropsychiatric symptoms.

Here we report the results of a prespecified secondary analysis examining the effect of citalopram on all individual domains assessed by the NPI. We hypothesized that individuals treated with citalopram, compared with those treated with placebo, would show improvements in neuropsychiatric symptoms beyond agitation, including affective (depression, apathy, anxiety, and irritability) and psychotic (delusions and hallucinations) symptoms.

METHOD

Study Population

The methods and primary results from CitAD have been described in detail elsewhere (19, 20). In brief, CitAD was an investigator-initiated, 9-week, randomized, double-blind, placebo-controlled multicenter clinical trial with two parallel treatment groups assigned in a 1:1 ratio and randomization stratified by treatment center.

To summarize, 186 study participants were diagnosed with probable Alzheimer's disease as defined by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria (26) and had Mini-Mental State Examination (27) scores ranging from 5 to 28. Additional inclusion criteria included "clinically significant agitation" for which a physician determined that medication was appropriate and which was rated as occurring "very frequently" or "frequently" with "moderate" or "marked" severity, as assessed by the agitation/aggression item of the NPI. Exclusion criteria included a current major depressive episode or psychosis requiring antipsychotic treatment. A readily available caregiver was required, to provide information for outcome measures and to supervise medication use. Stable dosages of medications for the treatment of Alzheimer's disease were allowed, but prerandomization withdrawal of psychotropic medications other than predefined rescue medications was required.

Recruitment occurred at eight academic centers, seven in the United States and one in Canada. After receiving a complete description of the study, participants gave consent if they were found by clinicians experienced in clinical dementia research to have capacity, and they gave assent if they were not fully capable of providing consent, with consent obtained from a legally authorized representative. Informed consent was also obtained from caregivers for the collection of caregiver measures. The study was conducted under the oversight of a data safety monitoring board. Institutional review boards at all study sites approved and monitored the study.

Intervention

Patients were randomized to receive citalopram at a target dosage of 30 mg/day, with planned titration over 3 weeks from a starting dosage of 10 mg/day, or matching placebo. During the first 3 weeks after randomization, clinicians could adjust the medication dosage according to response and tolerability (78% received 30 mg/day and 15% received 20 mg/day). In addition to pharmacotherapy, participants and caregivers received a standardized practical psychosocial intervention that consisted of three components: provision of educational materials, 24-hour availability of crisis management services, and a 20- to 30-minute counseling session at each scheduled study visit. Patients and caregivers completed in-person visits at baseline and at 3, 6, and 9 weeks.

Outcome Assessment

Primary efficacy measures were the agitation subscale of the Neurobehavioral Rating Scale (21) and the modified CGIC (22). Secondary efficacy measures included the NPI total score, the NPI caregiver distress score, individual NPI domain ratings, the short form of the Cohen-Mansfield Agitation Inventory (23), the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (25), and use of rescue lorazepam.

The present analysis examines the effects of citalopram treatment on neuropsychiatric symptoms in addition to agitation, as rated on the NPI, which was developed to assess the frequency and severity of behavioral disturbances in dementia and of caregiver distress resulting from them, as reported by the patient's caregiver. The NPI has well-established psychometric properties (23, 28) and wide acceptance in assessing neuropsychiatric symptoms in cognitive disorders (29). The 12 domains of the NPI are delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep/nighttime behavior disorders, and appetite/eating disorders. The frequency of each symptom is rated on a 4-point Likert scale (1=rarely/less than once per week, 2=sometimes/about once per week, 3=frequently/several times a week but less than every day, 4=very frequently/daily or continuously). The severity of each symptom present is rated on a 3-point Likert scale (1=mild/not distressing, 2=moderate/distressing

TABLE 1. Baseline Neuropsychiatric Inventory (NPI) Scores of Participants in a Study of the Effects of Citalopram on Neuropsychiatric Symptoms in Alzheimer's Dementia

	Total Sample (N=186)				Citalopram Group (N=94)				Placebo Group (N=92)			
	All Participants[a]		Participants Reporting Symptoms[b]		All Participants[a]		Participants Reporting Symptoms[b]		All Participants[a]		Participants Reporting Symptoms[b]	
NPI Measure	N	%	Median	IQR	N	%	Median	IQR	N	%	Median	IQR
Individual domains												
Delusions	78	42	4	3, 8	39	41	4	3, 8	39	42	4	2, 8
Hallucinations	39	21	3	1, 6	18	19	1.5	1, 4	21	23	3	2, 8
Agitation/aggression[c]	186	100	8	6, 8	94	100	8	6, 8	92	100	8	6, 9
Depression/dysphoria	95	51	3	2, 6	50	53	3	2, 6	45	49	3	2, 4
Anxiety	121	65	4	3, 8	61	65	4	3, 6	60	65	6	3, 8
Elation/euphoria	13	7	2	2, 4	9	10	2	2, 4	4	4	2	1.5, 2
Apathy/indifference	114	61	6	4, 8	58	62	6	4, 8	56	61	6	4, 8
Disinhibition	95	51	4	2, 6	49	52	4	2, 6	46	50	4	2, 6
Irritability/lability	157	84	6	6, 8	83	88	6	4, 8	74	80	6	6, 8
Aberrant motor behavior	96	52	8	4, 8	48	51	6	4, 8	48	52	8	4, 8
Sleep/nighttime behavior disorders	85	46	6	3, 8	40	43	6	3, 8	45	49	6	4, 8
Appetite/eating disorders	86	46	6	4, 8	49	52	6	4, 8	37	40	6	3, 8
Summary scores												
Nonmood score[c]	186	100	19.5	13, 25	94	100	18.5	12, 24	92	100	20	14, 26
Affective score	182	98	14	8, 20	91	97	14	9, 20	91	99	14	8, 20
Psychotic score	97	52	4	3, 8	49	52	4	3, 8	47	51	4	2, 8

[a] Number and percent refer to participants with a domain or summary score >0.
[b] Median and interquartile range (IQR) refer to frequency by severity score among participants reporting the symptom. Higher scores indicate more frequent and/or more severe symptoms.
[c] All participants reported agitation at enrollment, per study eligibility requirements.

but can be redirected, 3=marked/very distressing and difficult to redirect). A composite score is calculated for each symptom by multiplying the frequency and severity scores, yielding a domain score of 0 to 12. Alternatively, a dichotomous presence/absence definition can be used, with presence defined as a domain score >0 (2, 30). In both approaches, higher scores reflect greater symptom burden. In CitAD, the 12-item NPI was administered to the caregiver at baseline and at 3, 6, and 9 weeks.

Statistical Analysis

The distributions of the individual NPI domain scores were skewed and had a large number of zero values (indicating absence of a domain symptom), except for the agitation domain, because a set minimum NPI agitation domain score was a study inclusion criterion. Hence, standard methods for comparing the means of the individual domain scores were not appropriate. The baseline proportion of patients reporting each symptom and the median score among those who had the symptom are listed in Table 1. To compare the follow-up NPI scores, we used a two-part model (31) to compare the proportion of patients who had each symptom at week 9 and the distribution of domain scores only among those who had each symptom at week 9.

First, we compared the citalopram and placebo groups on the proportion who had symptoms at week 9 in each NPI domain, reflecting presence or absence. Presence of a symptom was defined as a domain score >0. Odds ratios of the symptoms being reported at week 9 for the citalopram group compared with the placebo group were estimated using a saturated means model (including indicators for each follow-up visit and visit-by-treatment group interactions) with generalized estimating equations; a logistic link function and a first-order autoregressive covariance structure were included, and the model was controlled for baseline symptom score and Mini-Mental State Examination score (which was not balanced at baseline between the two treatment groups). All available follow-up data were included. The primary comparison was the odds ratio at the week 9 visit. Second, we compared the domain score distributions at week 9 only for symptomatic patients (i.e., domain score >0 at week 9), reflecting the severity of the symptoms that were present. Because the domain scores were not distributed normally among the symptomatic patients, we compared distributions using exact Wilcoxon rank sum tests. Sensitivity analyses were performed by imputing missing data for all study visits using the method of multiple imputation (32) (see Table S1 in the data supplement that accompanies the online edition of this article).

RESULTS

The baseline characteristics were similar between the citalopram and placebo groups, except that the placebo group had a lower mean score on the Mini-Mental State Examination (20). In addition to agitation, several other neuropsychiatric symptoms were frequently reported at baseline (Table 1). There was no significant difference between the

TABLE 2. Neuropsychiatric Inventory (NPI) Domains at Week 9 in a Study of the Effects of Citalopram on Neuropsychiatric Symptoms in Alzheimer's Dementia

	All Participants With Week 9 NPI Data							Participants With Week 9 NPI Data Reporting Symptom at Week 9				
	Citalopram Group (N=86)		Placebo Group (N=83)					Citalopram Group		Placebo Group		
NPI Measure	N[a]	%	N[a]	%	Odds Ratio[b]	95% CI	p	Median	IQR	Median	IQR	p[c]
Individual domains												
Delusions	22	26	35	42	0.40	0.18, 0.91	0.03	4	2, 8	4	3, 8	0.46
Hallucinations	11	13	13	16	1.53	0.50, 4.71	0.46	1	1, 3	6	4, 6	<0.01
Agitation/aggression	66	77	70	84	0.63	0.28, 1.41	0.26	3	2, 8	6	3, 8	0.05
Depression/dysphoria	24	28	30	36	0.69	0.34, 1.39	0.30	3	1, 6	3	2, 6	0.35
Anxiety	36	42	54	65	0.43	0.22, 0.84	0.01	4	2.5, 8	4	3, 6	0.78
Elation/euphoria	3	3	5	6	0.45	0.09, 2.21	0.32	1	1, 8	3	2, 6	0.55
Apathy/indifference	41	48	42	51	0.92	0.47, 1.80	0.82	4	3, 8	6	4, 8	0.36
Disinhibition	27	31	34	41	0.71	0.35, 1.46	0.35	4	2, 8	4	2, 6	0.73
Irritability/lability	49	57	61	73	0.38	0.19, 0.76	0.01	4	2, 6	6	3, 8	0.13
Aberrant motor behavior	34	40	47	57	0.49	0.24, 0.99	0.05	4	3, 8	4	3, 8	0.96
Sleep/nighttime behavior disorders	21	24	30	36	0.56	0.27, 1.16	0.12	4	3, 12	3	2, 6	0.03
Appetite/eating disorders	22	26	18	22	1.32	0.62, 2.82	0.47	4	4, 8	4	3, 8	0.84
Summary scores												
Nonmood score	78	91	79	95	0.48[d]	0.10, 2.00	0.41	8.5	5, 17	14	8, 24	<0.01
Affective score	72	84	78	94	0.33	0.11, 1.03	0.06	7	4, 14.5	12	6, 20	0.04
Psychotic score	28	33	37	45	0.67	0.31, 1.44	0.30	4	2, 6	6	4, 9	0.02

[a] Number and percent refer to participants reporting the symptom at week 9.
[b] The odds ratio is calculated using generalized estimating equations including all follow-up visits with a logistic link and first-order autoregressive covariance structure. The estimate shown is for the odds of reporting the symptoms at week 9 for citalopram compared with placebo, controlling for baseline symptom score and Mini-Mental State Examination score. Numbers <1 favor citalopram.
[c] The p values were calculated by exact Wilcoxon test (rank sum).
[d] Exact logistic using week 9 data only.

citalopram and placebo groups in baseline frequency or severity (in patients who had symptoms at baseline) for any neuropsychiatric symptom domain. Agitation/aggression was present in 100% of the sample, as agitation was a study inclusion criterion. The other most common neuropsychiatric symptoms at baseline were irritability/lability (84%), anxiety (65%), apathy/indifference (61%), aberrant motor behavior (52%), disinhibition (51%), and depression/dysphoria (51%). Among participants reporting a particular symptom at baseline, the domains with the highest median scores were agitation/aggression (median=8), aberrant motor behavior (median=8), irritability/lability (median=6), apathy/indifference (median=6), sleep/nighttime behavior disorders (median=6), and appetite/eating disorders (median=6). Median scores for depression/dysphoria were low (median=3), as a current major depressive episode was a study exclusion criterion. Similarly, median scores for delusions and hallucinations were low, as the study excluded patients with psychosis requiring antipsychotics. For participant flow through the study, see the Figure S1 in the online data supplement.

By week 9, several differences between the citalopram and placebo groups were evident (Table 2). Participants in the citalopram group were significantly less likely to have reports of delusions (odds ratio=0.40, 95% CI=0.18, 0.91, p=0.03), anxiety (odds ratio=0.43, 95% CI=0.22, 0.84, p=0.01), and irritability/lability (odds ratio=0.38, 95% CI=0.19, 0.76, p=0.01) compared with those in the placebo group. By week 9, 24% in the citalopram group and 36% in the placebo group had sleep/nighttime behavior disorders, compared with 43% and 49%, respectively, at baseline, a nonsignificant difference. Median domain scores among the patients with reports of a symptom at week 9 were lower in the citalopram group compared with the placebo group for hallucinations (median=1 [interquartile range (IQR)=1, 3] compared with median=6 [IQR=4, 6]); p≤0.01), but higher for sleep/nighttime behavior disorders (median=4 [IQR=3, 12] compared with median=3 [IQR=2, 6]); p=0.03).

The primary outcome measures of CitAD were the effect of citalopram on agitation as assessed by the Neurobehavioral Rating Scale and the modified CGIC. In this secondary analysis using the NPI, participants in the citalopram group were as likely as those in the placebo group to have reports of agitation/aggression at week 9 (odds ratio=0.63, 95% CI=0.28, 1.41, n.s.). Among participants with reports of agitation/aggression at week 9, the median domain scores were lower in the citalopram group, but the difference failed to reach statistical significance (median=3 [IQR=2, 8] compared with median=6 [IQR=3, 8]); p=0.05). The results were similar for the models using multiply imputed data.

To further explore these results, we looked at emergence of behavioral symptoms at week 9 when they were not present at baseline as well as the percentage of participants who responded and remitted by week 9 in the behavioral

TABLE 3. Presence of Symptoms at Week 9 Versus at Baseline in a Study of the Effects of Citalopram on Neuropsychiatric Symptoms in Alzheimer's Dementia

	Symptom Present at Baseline											
	Total Sample (N=186)				Citalopram Group (N=94)				Placebo Group (N=92)			
	No		Yes		No		Yes		No		Yes	
Symptom Present at Week 9	N	%	N	%	N	%	N	%	N	%	N	%
Delusions	108	58	78	42	55	59	39	41	53	58	39	42
Missing	11	10	6	8	5	9	3	8	6	11	3	8
No	90	83	22	28	48	87	16	41	42	79	6	15
Yes	7	7	50	64	2	4	20	51	5	10	30	77
Anxiety	65	35	121	65	33	35	61	65	31	35	60	65
Missing	7	11	10	9	3	9	5	8	4	12	5	8
No	41	63	38	31	24	73	26	43	17	54	12	20
Yes	17	26	73	60	6	18	30	49	11	34	43	72
Irritability/lability	29	16	157	84	11	12	83	88	18	20	74	80
Missing	3	11	14	9	2	18	6	7	1	6	8	11
No	17	58	42	27	5	45	32	39	12	67	10	14
Yes	9	31	101	64	4	37	45	54	5	27	56	75

TABLE 4. Presence of Symptoms at Baseline Versus Symptom Status at Week 9 in a Study of the Effects of Citalopram on Neuropsychiatric Symptoms in Alzheimer's Dementia

	Total Sample (N=186)						Citalopram Group (N=94)						Placebo Group (N=92)					
Symptom Present at Baseline	Missing at Week 9		Score Improved ≥50% at Week 9		Resolved at Week 9		Missing at Week 9		Score Improved ≥50% at Week 9		Resolved at Week 9		Missing at Week 9		Score Improved ≥50% at Week 9		Resolved at Week 9	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Delusions (N=78)	6	8	36	46	22	28	3	8	21	54	16	41	3	8	15	38	6	15
Anxiety (N=121)	10	8	60	50	38	31	5	8	35	57	26	43	5	8	25	42	12	20
Irritability/lability (N=157)	14	9	85	54	42	27	6	7	53	64	32	39	8	11	32	43	10	14

domains of delusions, anxiety, and irritability/lability in participants with symptoms at baseline. Emergence of delusions was relatively rare but was more frequent in the placebo group (4% in the citalopram group, compared with 10% in the placebo group). Emergence of anxiety was more common and again was seen more frequently in the placebo group (18% compared with 34%). Emergence of irritability was harder to ascertain, as over 80% of the study population had those symptoms at baseline. It appears that emergence of irritability was common (37% and 27% in the citalopram and placebo groups, respectively) (Table 3). For those participants who had symptoms at baseline, treatment response was defined as a reduction ≥50% in the total domain score on the NPI, and remission as a total domain score of 0 at week 9. Again, for delusions, anxiety, and irritability, greater proportions of the citalopram group responded and remitted. The percentage difference between the citalopram and placebo groups in the three behavioral domains ranged from 15% to 21% for response and from 23% to 26% for remission (Table 4).

The participants who showed benefit from citalopram on this broad range of concomitant neuropsychiatric symptoms have limited overlap with those participants who responded in terms of clinical measures of agitation. While the correlations are statistically significant, they are of a small magnitude (analysis not shown).

DISCUSSION

We examined the effects of citalopram on neuropsychiatric symptoms in patients with Alzheimer's disease and clinically significant agitation, with the hypothesis that participants treated with citalopram would show broad improvement over those treated with placebo in individual NPI domains beyond agitation. Indeed, the citalopram group was less likely to have reports of delusions, anxiety, or irritability/lability after 9 weeks of treatment compared with the placebo group. The domain scores (reflecting severity of symptoms) for those with reported symptoms at week 9 showed superiority of citalopram for hallucinations in patients who had hallucinations at week 9 but superiority of placebo for sleep/nighttime behavior disorders in the roughly 45% of patients who had these problems at week 9. The patients enrolled in the CitAD study could not have psychotic symptoms that required treatment with antipsychotics, and it should be noted that only 19% and 23% in the citalopram and placebo groups, respectively, had hallucinations at baseline, and 13% and 16% at week 9; baseline median scores were very low, at

1.5 and 3, and at week 9 they were 1 and 6. Thus, it is uncertain whether these findings apply to a patient population with Alzheimer's disease and agitation in whom psychotic symptoms are more severe.

The present findings are consistent with those of previous studies showing improvement in anxiety and irritability with citalopram in patients with Alzheimer's disease exhibiting neuropsychiatric symptoms (17, 33). The improvement observed in delusions is congruent with previous reports of associations between serotonin loss and psychosis in Alzheimer's disease and with studies suggesting that citalopram may be efficacious in treating these symptoms. Furthermore, polymorphism of 5-HT_{2A}, 5-HT_{2C}, and the 5-HT transporter are linked to psychosis in Alzheimer's disease (33–36). Pimavanserine, a selective 5-HT_{2A} inverse agonist, was recently reported to benefit patients with Parkinson's disease psychosis (37).

While a reduction in the proportion of patients with an NPI domain score >0 for sleep/nighttime behavior disorders was seen overall in the citalopram group and the median domain score among those with symptoms decreased, it appears that some patients in the citalopram group had worsening of these symptoms, consistent with known SSRI-mediated adverse effects. Conversely, insomnia was reported more frequently as an adverse event in the placebo group (45.3%, compared with 31.1% in the citalopram group) (20).

We did an exploratory analysis on responder and remission status at week 9 in those participants who had symptoms at baseline in the domains of delusions, anxiety, and irritability/lability, and emergence of symptoms in the same domains in those participants who had no symptoms at baseline. Treatment with citalopram was associated with more frequent response (defined as a reduction ≥50% in symptom score) and remission in all three domains and reduced emergence of delusions and anxiety. For irritability/lability, emergence appeared common, but the vast majority of participants already had those symptoms at baseline, making the results harder to interpret. Overall, it appears that treatment with citalopram at 30 mg/day was clinically important in those domains, but this finding requires confirmation in future studies, as the dosage used in this study is higher than what should be used in clinical practice in this patient population. Current prescribing information recommends a maximum daily dose of 20 mg of citalopram for patients over age 60. This trial did not have enough patients treated with 20 mg/day to assess efficacy at that dosage level. The benefit of citalopram for individual behavioral domains or overall agitation at lower dosages is not known.

Data on tolerability in CitAD were reported in the primary analysis (20), which noted that there was no difference in adherence between the citalopram and placebo groups and that side effects were generally modest and consistent with those known to be associated with SSRIs (gastrointestinal complaints, respiratory tract infections, and falls). The adverse effects of cognitive worsening (of unknown clinical significance) and QT prolongation, however, raise concern about the 30 mg/day dosage used. The QT findings have been reported elsewhere (38), and the cognitive findings will be examined in further detail in subsequent analyses. While the present findings suggest that it is reasonable to expect a positive impact of citalopram on other neuropsychiatric symptoms in patients with Alzheimer's disease and agitation, particularly anxiety, irritability/lability, and delusions, caution in the use of citalopram is advised.

One notable limitation of the trial is that it was powered to detect differences in the primary outcome measure but not in the several secondary and exploratory outcome measures, including the NPI total score and individual domain scores, leading to small numbers in some of the subanalyses. Furthermore, statistical correction for multiple comparisons was not implemented. Thus, the findings should be considered exploratory. Among other limitations were no dose range information; participants comprised a convenience sample in U.S. and Canadian academic medical centers that may not generalize to other settings; the duration of treatment was short; the effect of citalopram on neuropsychiatric symptoms in non-Alzheimer's dementia remains unknown; and the effect of citalopram on neuropsychiatric symptoms in Alzheimer's disease without agitation remains unknown.

CONCLUSIONS

Establishing treatments for neuropsychiatric symptoms in Alzheimer's disease that are both safe and efficacious remains a challenge. Citalopram at a dosage of 30 mg/day shows efficacy for the treatment of agitation (19) and appears to be similarly effective for a broad range of concomitant neuropsychiatric symptoms, particularly delusions, anxiety, and irritability/lability. While citalopram is a therapeutic option for the treatment of agitation in Alzheimer's disease even when psychotic symptoms are present, the concerning side effects of cognitive worsening and delayed cardiac repolarization seen in this study as well as safety concerns with depressed elderly patients (16), urge dosage constraints and caution. The benefit of citalopram for individual behavioral domains or overall agitation at lower dosages is not known and requires further study before widespread use in this patient population.

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Supported by National Institute on Aging (NIA) and NIMH grant R01AG031348, and in part by NIH grant P50-AG05142 (to University of Southern California and Dr. Schneider).

Dr. Devanand has received research support from Avanir and has served on scientific advisory boards for AbbVie, Astellas, and Lundbeck and as a consultant for Intracellular Therapies. Dr. Munro has received grant funding (to her institution) from NIA, NIH, and NIMH and has received payment for expert testimony from various law firms, from the Office of the Federal Public Defender, and from the U.S. Attorney's Office, as well as payment for lectures for Episcopal Ministries. Dr. Mintzer has received grant support from and served as a consultant for Avanir Pharmaceuticals, Transition Therapeutics, and Insys Therapeutics; he has received support for travel to meetings from NIA and NIMH; he has received grants (to his institution) from NIA, NIH, Takeda Global Research and Development Center, Pfizer, Genentech, Merck, Accera, Elan, Avanir, Hoffmann-La Roche, Novartis, Baxter, Eli Lilly, Wyeth, and Janssen Alzheimer Initiative; he has been employed by NeuroQuest and is founder of BioPharma Connex. Dr. Pollock has received a grant (to his institution) from NIA and NIMH; he has served on a board for Lundbeck Canada and as a consultant for Wyeth; and he has received travel and accommodation support from Lundbeck International Neuroscience Foundation. Dr. Rosenberg has received grant support from the Alzheimer's Assocation, Eli Lilly, Functional Neuromodulation, Merck, NIA, and Novartis; he has served as a consultant to AbbVie, Abide, Insys, Janssen, and Merck; and he has received travel support from Eli Lilly. Dr. Schneider has received grant and clinical trial support from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Merck, NIH, Novartis, Pfizer, and Roche and consultancy fees, including for data monitoring committees and adjudication committees, from Abbott, AbbVie, ACImmune, AstraZeneca, Baxter, Bristol-Myers Squibb, Elan, Eli Lilly, Forest Laboratories, Forum, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Merck, Merz, Novartis, Orion, Otsuka, Pfizer, Roche, Servier, Takeda, Toyama/FujiFilm, and Zinfandel. Dr. Weintraub has received research funding or support from the Michael J. Fox Foundation for Parkinson's Research, NIH, Novartis, the Department of Veterans Affairs, Avid Radiopharmaceuticals, the Alzheimer's Disease Cooperative Study, and the International Parkinson and Movement Disorder Society; honoraria from AbbVie, Acadia, Biotie, Clintrex, Novartis, Teva Pharmaceuticals, UCB, and the CHDI Foundation; license fee payments from the University of Pennsylvania for the QUIP and QUIP-RS; royalties from Wolters Kluwer; and fees for legal consultation for a lawsuit related to antipsychotic prescribing in a patient with Parkinson's disease. Dr. Lyketsos has received grant support (for research or CME) from NIMH, NIA, the Associated Jewish Federation of Baltimore, the Weinberg Foundation, Forest, GlaxoSmithKline, Eisai, Pfizer, AstraZeneca, Eli Lilly, Ortho-McNeil, Bristol-Myers Squibb, Novartis, the National Football League, Elan, and Functional Neuromodulation; he has served as a consultant or adviser to AstraZeneca, GlaxoSmithKline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Eli Lilly, Pfizer, Genentech, Elan, the NFL Players Association, the NFL Benefits Office, Avanir, Zinfandel, Bristol-Myers Squibb, AbbVie, Janssen, Orion, Otsuka, and Astellas; and he has received honoraria or travel support from Pfizer, Forest, GlaxoSmithKline, and Health Monitor. Dr. Porsteinsson has received grants (to his institution) from AstraZeneca, Avanir, Baxter, Biogen, Bristol-Myers Squibb, Eisai, Elan, EnVivo, Genentech/Roche, the Janssen Alzheimer Initiative, Medivation, Merck, Pfizer, Toyama, Transition Therapeutics, NIH, NIMH, NIA, and the Department of Defense; he has served as a consultant for Elan, the Janssen Alzheimer Initiative, Lundbeck, Pfizer, and TransTech Pharma; and he has been a member on data safety and monitoring boards for Quintiles, Functional Neuromodulation, and the New York State Psychiatric Institute, participated on a speakers bureau for Forest, and participated in the development of educational presentations for CME, Inc., and PVI. The other authors report no financial relationships with commercial interests.

ClinicalTrials.gov identifier: NCT00898807.

Received Feb. 24, 2015; revision received Jan. 10, 2016; accepted Jan. 26, 2016.

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