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Citalopram for the Treatment of Agitation in Alzheimer Dementia: Genetic Influences

Matthew E. Peters, MD¹, Vijay Vaidya, MPH², Lea T. Drye, PhD², Davangere P. Devanand, MD³, Jacobo E. Mintzer, MD⁴, Bruce G. Pollock, MD, PhD^{5,6}, Anton P. Porsteinsson, MD⁷, Paul B. Rosenberg, MD¹, Lon S. Schneider, MD⁸, David M. Shade, JD², Daniel Weintraub, MD⁹, Jerome Yesavage, MD¹⁰, Constantine G. Lyketsos, MD, MHS¹, Dimitri Avramopoulos, MD, PhD¹, and For the CitAD Research Group

¹Johns Hopkins University School of Medicine, Baltimore, MD, USA

²Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

³Columbia University Medical Center, New York, NY, USA

⁴Medical University of South Carolina, Charleston, SC, USA

⁵Centre for Addiction and Mental Health, Campbell Family Institute, Toronto, Canada

⁶University of Toronto, Toronto, Canada

⁷University of Rochester School of Medicine, Rochester, NY, USA

⁸Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

⁹University of Pennsylvania School of Medicine, Philadelphia, PA, USA

¹⁰Stanford University School of Medicine, Stanford, CA, USA

Abstract

Objective—To assess potential genetic influences on citalopram treatment efficacy for agitation in individuals with Alzheimer dementia (AD). Six functional genetic variants were studied in the following genes: serotonin receptor 2A (*HTR2A*-T102C), serotonin receptor 2C (*HTR2C*-Cys23Ser), serotonin transporter (*5HTT*-LPR), brain-derived neurotrophic factor (BDNF-Val66-Met), apolipoprotein E (ε2, ε3, ε4 variants), and cytochrome P450 (*CYP2C19*). Treatment response by genotype was measured by (1) the agitation domain of the Neurobehavioral Rating Scale, (2) the modified Alzheimer Disease Cooperative Study—Clinical Global Impression of Change scale (mADCS-CGIC), (3) the agitation domain of the Neuropsychiatric Inventory (NPI), and (4) the Cohen-Mansfield Agitation Inventory.

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Corresponding Author: Constantine G. Lyketsos, Johns Hopkins University School of Medicine, 5300 Alpha Commons Drive, Baltimore, MD 21224, USA., kostas@jhmi.edu.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article

Method—We utilized data from the Citalopram for Agitation in Alzheimer’s Disease (CitAD) database. CitAD was a 9-week randomized, double-blind, placebo-controlled multicenter clinical trial showing significant improvement in agitation and caregiver distress in patients treated with citalopram. Proportional odds logistic regression and mixed effects models were used to examine the above-mentioned outcome measures.

Results—Significant interactions were noted on the NPI agitation domain for *HTR2A* (likelihood ratio [LR] = 6.19, $df = 2$, $P = .04$) and the mADCS-CGIC for *HTR2C* (LR = 4.33, $df = 2$, $P = .02$) over 9 weeks.

Discussion—Treatment outcomes in CitAD showed modest, although statistically significant, influence of genetic variation at *HTR2A* and *HTR2C* loci. Future studies should continue to examine the interaction of known genetic variants with antidepressant treatment in patients with AD having agitation.

Keywords

Alzheimer disease; citalopram; agitation; randomized trial; dementia; antidepressant; genetics

Introduction

Alzheimer disease (AD), the most common cause of dementia, affects over 5 million persons in the United States as of 2013.¹ Alzheimer disease is marked by progressive neurodegeneration resulting in cognitive deficits and neuropsychiatric symptoms (NPSs).² Agitation, an NPS that is often chronic, may be seen at any level of dementia severity.^{3–5} Agitation has detrimental effects on quality of life and may lead to increased caregiver burden, dangerous behaviors, institutionalization, and use of restraints.⁶

The Citalopram for Agitation in Alzheimer’s Disease (CitAD) study was a 9-week randomized, double-blind, placebo-controlled multicenter clinical trial designed to investigate the efficacy and safety of the selective serotonin reuptake inhibitor (SSRI) citalopram for agitation in AD.⁷ In the primary results from the trial, citalopram was found to be efficacious for treatment of agitation in AD.⁸ Additional analyses looking at citalopram’s effect on other NPS in AD during this trial are ongoing.

Genetic research focused on the development, severity, and treatment of mental disorders is of growing interest. Genetic research on mental disorders in the geriatric population, including the influence of genetics on SSRI response, has shown varied results in regard to age, the overall effect of genetics, and genetic effects on particular drugs and particular disease processes.^{9–19}

We hypothesized that CitAD participants with certain genetic backgrounds might be more likely to respond to citalopram and conducted genetic analyses on 6 genes for which polymorphisms have been associated with response to antidepressant treatment: 2 serotonin receptor genes (*HTR2A* and *HTR2C*), the serotonin transporter gene (*SLC6A4*, best known as *5HTT*), the brain-derived neurotrophic factor gene (*BDNF*), the apolipoprotein E gene (*APOE*), and the cytochrome P450 2C19 gene (*CYP2C19*). Specific polymorphisms in these genes were genotyped. *HTR2A*-T102C is a single-nucleotide polymorphism (SNP; dbSNP

ID: rs6313) that has been associated with psychosis and depression in AD.^{10,14} *HTR2C*-Cys23Ser (dbSNP ID: rs6318) is a coding nonsynonymous SNP known to influence levels of monoamines in the brain, especially norepinephrine.¹¹ *5HTT*-LPR is a common functional insertion/deletion polymorphism found in the promoter region of the *5HTT* gene that has been associated with efficacy of antidepressant treatments in the elderly individuals.^{12,13,15} *BDNF*-Val66Met is a coding nonsynonymous SNP (dbSNP ID: rs6265) that has been associated with efficacy of antidepressant treatment in the elderly individuals¹⁷ as well as with AD-related depression.²⁰ The APOE protein ϵ 2, ϵ 3, ϵ 4 allelic variants result from 2 coding nonsynonymous SNPs (dbSNP IDs: rs429358 and rs7412) and have been extensively studied in relationship with risk of AD.²¹ More recent interest has focused on the impact of the ϵ 4 allelic variant on response to lipid-lowering treatment^{22,23} and antidepressant response.¹⁸ *CYP2C19* is known to have variants associated with the metabolism and clearance of citalopram and escitalopram,¹⁹ leading to lower or higher serum concentrations of the drug. It is important to remember that as opposed to most of the genetic studies that have looked at how genes affect the efficacy of antidepressants for treating depressive syndromes, the present study looks at the efficacy of using an antidepressant for treatment of agitation in dementia.

We report on citalopram efficacy in genetically defined subgroups of participants. Specifically, we differentiated participants based on polymorphisms in the 6 genes listed earlier. We examined treatment response by genotype as measured by (1) the agitation domain of the Neurobehavioral Rating Scale (NBRSA), (2) the modified Alzheimer Disease Cooperative Study—Clinical Global Impression of Change scale (mADCS-CGIC), (3) the agitation domain of the Neuropsychiatric Inventory (NPI), and (4) the Cohen-Mansfield Agitation Inventory (CMAI).

Method

Study Population

We utilized data from the CitAD study, a 9-week randomized, double-blind, placebo-controlled multicenter clinical trial, with 2 parallel treatment groups assigned in a 1:1 ratio and randomization stratified by clinical center. The methods⁷ and primary results⁸ of CitAD have been detailed elsewhere. The study was conducted under the oversight of an independent Data Safety Monitoring Board.

To summarize, study participants were diagnosed with probable AD as defined by the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria²⁴ and had Mini-Mental State Examination (MMSE)²⁵ scores of 5 to 28 inclusive. Additionally, participants had "clinically significant agitation" for which a physician has determined that a medication is appropriate and that is rated as occurring "frequently" with "moderate" or "marked" severity as assessed by the agitation and/or aggression items of the Neuropsychiatric Inventory (NPI).²⁶

Recruitment occurred at memory clinics, geriatric psychiatry clinics, Veterans Administration geriatric clinics, nursing homes, community outreach, advertising, and

Alzheimer Disease Research Centers associated with 7 US and 1 Canadian clinical centers and 2 resource centers (the chair's office and the coordinating center). Participants gave consent if found to have capacity by clinicians experienced in clinical dementia research and assent if not fully capable of providing consent (with consent obtained from an authorized legal representative). Informed consent was also obtained from caregivers for the collection of caregiver measures.

Procedure

Participants were randomized in a 1:1 ratio to receive (1) citalopram (target dose: 30 mg/d) or (2) placebo. During the first 3 weeks postrandomization, clinicians could adjust the dosage of the medication according to response and tolerability. In addition to pharmacotherapy, a trained study clinician conducted a standardized and practical psychosocial intervention with the participants and caregivers 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. Patients and caregivers completed in-person visits at baseline, 3, 6, and 9 weeks postrandomization. At week 9, all patients were unmasked.

Genetic Analyses

Blood draws for DNA extraction were performed at the baseline in-person visit. DNA was extracted using the Gentra Puregene Blood Kit from Qiagen (cat# 158389; Germantown, Maryland) and following the manufacturer's protocol. Genotyping was performed by the TaqMan method utilizing the assays on demand product from Applied Biosystems (Carlsbad, California). Exceptions were *5HTT*-LRP, *BDNF*-Val66Met, and *APOE*. *5HTT*-LRP was genotyped after polymerase chain reaction amplification with primers GCGTTGCCGCTCTGAATGC and GAGGGACTGAGCTGGACAACCAC at an annealing temperature of 60°C and electrophoresis on a 2.5% agarose—1% nusieve gel for separation of the short and long allelic variants. *BDNF*-Val66Met was genotyped by *Nla*III digestion after PCR amplification with primers ACTCTGGAGAGCGTGAAT and ATACTGTCACACACGCTC and electrophoresis as mentioned earlier. *APOE* genotyping was performed as in Avramopoulos et al.²⁷ Assignment to metabolizer categories for *CYP2C19* was performed as in Jin et al.¹⁹

Outcomes Assessment

Primary efficacy measures were the agitation subscale of the NBR²⁸ (range 0–18 with higher scores indicating more severe symptoms) and the mADCS-CGIC²⁹ (range 1–7 with 1 indicating marked improvement and 7 indicated marked worsening from baseline). Secondary efficacy outcomes measures significant here included the NPI²⁶ total score (frequency by severity range 0–144 with higher scores indicating more severe symptoms), the individual NPI domain of Agitation/Aggression, and the CMAI³⁰ (range 14–70 with higher scores indicating more severe symptoms).

Analysis

The statistical analysis for the overall treatment effect for NBRS, mADCS-CGIC, NPI, and CMAI has been described in detail previously.⁸ The participants who provided DNA were compared on demographic and prognostic characteristics between the 2 treatment groups. Similarly, the participants who did not provide DNA sample were compared with DNA providers to see the differences between the 2 groups. The genetic variant distribution between the 2 treatment groups was also compared. Kruskal-Wallis test was used for continuous variables, and χ^2 or Fisher exact test was used for categorical variables.

Treatment effects were evaluated according to intention-to-treat principle. Mixed effects models with a random intercept that allowed the baseline scores for the patients to differ was used to compare the linear slopes between 2 treatment groups for CMAI agitation scores, NPI agitation scores, and NBRS agitation score over the 9-week period. The difference in the linear slopes due to genetic variation was tested by comparing the model that included Treatment $\times$ Time $\times$ Subgroup interaction with random intercept for patient and allowing the change over time to differ by subgroup and treatment. Likelihood ratio test statistic was used to compare the 2 models. Both models included baseline MMSE as covariate due to imbalance at baseline and adjusted for the baseline outcome score. As *HTR2C* is an X-linked gene, sex was included as a covariate in the model for *HTR2C*.

The mADCS-CGIC rating of change scale score was categorized into responders (moderate or marked improvement in mood) versus nonresponders (minimal improvement to marked worsening in mood) at weeks 3, 6, and 9. Multivariate normal approach was used to impute the missing values on mADCS-CGIC to be consistent with the results reported in the primary publication of the trial. Generalized estimating equations logistic regression was used to compare the proportions of responders in the 2 treatment groups over time. The subgroups differences due to genetic variation were tested by adding interaction term for Subgroup $\times$ Treatment $\times$ Time interaction with baseline MMSE score as covariate. Statistical analysis and graphs were performed using SAS version 9.4 (2002–2012 by SAS Institute Inc, Cary, North Carolina). As this was an exploratory study, *P* values were not adjusted for multiple comparisons.

Results

Of the 186 patients involved in the study, 176 (95%) consented to genetic testing and DNA banking. Of the 176 patients who provided consent, blood was collected and genotyping was performed on 175 (99%) patients.

Table 1 shows the baseline characteristics of the CitAD patients who provided a DNA sample and thus were included in this study. Participants assigned to citalopram group had significantly higher MMSE scores at baseline than those assigned to placebo (*P* = .03). Patients who agreed to provide blood for DNA were similar to patients who refused to provide blood for DNA with respect to baseline demographic and clinical characteristics (no statistically significant differences). Table 2 compares allele distribution between the citalopram and placebo groups for each gene. No significant differences in distribution were seen between the two groups for any of the polymorphisms analyzed.

Table 3 shows the resulting likelihood ratios (LR) and chi-square (χ^2) statistics for test of interactions analyses for each of the genetic polymorphisms analyzed. Significant interactions were noted on the NPI agitation domain for *HTR2A* (LR = 6.19, df = 2, P = .04) and the mADCS-CGIC for *HTR2C* (LR = 4.33, df = 2, P = .02). *HTR2A* did not exhibit a monotonic effect for NPI agitation domain, and the test for linear trend was not significant. *HTR2C* exhibited monotonic effect on mADCS-CGIC remission outcome with the magnitude of treatment effect (citalopram vs placebo) decreasing in the following order: effect in AA > effect in AC > effect in CC. *HTR2C* variants did not modify the treatment effect on the agitation-specific outcomes in the study (CMAI, NBRS, and NPI agitation domain).

Discussion

The present study noted 2 significant genetic interactions when using citalopram to treat agitation in AD: (1) the *HTR2A*-T102C SNP on the NPI agitation domain and (2) the *HTR2C*-Cys23Ser SNP on the mADCS-CGIC. Of the 2, only the *HTR2C* interaction showed a monotonic effect. *HTR2C* showed no significant interactions with the agitation-specific measures in the study. There were no significant effects of allelic variants and polymorphisms in *5HTT*, *BDNF*, *APOE*, and *CYP2C19*.

Using 2 primary outcome measures (NBRS and mADCS-CGIC), we previously reported significant improvement in agitation in AD when participants were treated with citalopram.⁸ The present study, which shows some modest, although statistically significant, improvements based on genetic variants should be interpreted carefully. *HTR2A*, although significantly associated with one measure of agitation (NPI), was not associated with the NBRS or CMAI. One reason could be that agitation is a complex entity that is being measured slightly differently on each of the scales. For both *HTR2A* and *HTR2C*, the analyses were not adjusted for multiple comparisons, and thus some statistical significance may be expected by chance alone.

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 and a high rate of adherence to study drug, (4) careful definition of agitation of moderate or high severity, (5) relatively few medical or medication exclusions resulting in a study population that is broadly representative of patients with AD, (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-AD 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. More specifically, for the analyses presented here, we did not control for multiple comparisons.

Conclusions

This study adds to the existing literature on the use of antidepressants for agitation in AD as well as to the literature on the influence of genetic variants on antidepressant response. Studies such as the present that examine genetic influences on treatment response (pharmacogenomics) are increasingly utilized in general and specialty populations with the hope that pharmacogenomics associations will be useful for predicting treatment response or choosing subgroups particularly likely to respond. Some question whether enough is currently known about how different etiologies and organic changes contribute to complex syndromes, such as depression, that genetic studies can prove clinically useful.³¹ Future studies should continue to examine treatment effects of antidepressants in larger population. In addition, analysis of other genetic variants associated with citalopram response is warranted.

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Table 1

Baseline Characteristics of Citalopram for Agitation in Alzheimer's Disease Study Patients Who Provided DNA Sample.

Characteristics	Overall (n = 175)	Citalopram (n = 91)	Placebo (n = 84)	P Value
Age, years				.78
Median	80.0	80.0	80.0	
First/third quartile	72.0/85.0	72.0/85.0	72.0/84.0	
Sex, %				.90
Male	95 (54.3)	49 (53.8)	46 (54.8)	
Female	80 (45.7)	42 (46.2)	38 (45.2)	
Ethnicity/race, %				.72
White, non-Hispanic	126 (72.0)	64 (70.3)	62 (73.8)	
African American	29 (16.6)	15 (16.5)	14 (16.7)	
Asian	6 (3.4)	3 (3.3)	3 (3.6)	
Pacific Islander/ Hawaiian	2 (1.1)	2 (2.2)	0 (0)	
Other	12 (6.9)	7 (7.7)	5 (5.9)	
Marital status, %				.64
Married	106 (60.6)	55 (60.4)	51 (60.7)	
Widowed	45 (25.7)	21 (23.1)	24 (28.6)	
Separated	1 (0.5)	1 (1.1)	0 (0)	
Divorced	11 (6.3)	6 (6.6)	5 (5.9)	
Never married	12 (6.9)	8 (8.8)	4 (4.8)	
Dementia duration, years				.77
Median	4.0	4.0	3.5	
First/third quartile	2.0/7.0	2.0/7.0	2.0/7.0	
MMSE				.03
Median	16.0	18.0	14.0	
First/third quartile	10.0/22.0	13.0/22.0	8.0/20.5	
NBRS-Agitation				.13
Median	8.0	7.0	8.0	
First/third quartile	5.0/10.0	5.0/9.0	5.0/10.0	
CMAI				.37
Median	27.0	27.0	27.0	
First/third quartile	23.0/32.0	22.0/32.0	23.0/31.5	
NPI-Agitation				.67
Median	8.0	8.0	8.0	
First/third quartile	6.0/8.0	6.0/8.0	6.0/9.0	
NPI-Total Score				.93
Mean	34.0	33.0	34.0	
First/third quartile	24.0/47.0	24.0/47.0	24.5/47.5	

Abbreviations: MMSE, Mini-Mental State Examination; NBRs, Neurobehavioral Rating Scale; CMAI, Cohen-Mansfield Agitation Inventory; NPI, Neuropsychiatric Inventory.

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Table 2

Genotype Distribution Among 2 Treatment Groups.

Characteristics	Overall (n = 175)	Citalopram (n = 91)	Placebo (n = 84)	P Value
APOE-ε4 Allele				.21
Missing	25 (14.3)	13 (14.3)	12 (14.3)	
No ε4	65 (37.1)	30 (33.0)	35 (41.7)	
1 ε4	85 (48.6)	48 (52.7)	37 (44.0)	
HTR2A, %				.82
Missing	31 (17.7)	16 (17.5)	15 (17.9)	
CC	31 (17.7)	15 (16.5)	16 (19.0)	
CT	68 (38.9)	35 (38.5)	33 (39.3)	
TT	45 (25.7)	25 (27.5)	20 (23.8)	
<i>HTR2C</i> , male, % ^a				.75
Missing	16 (17.0)	8 (16.7)	8 (17.4)	
A	67 (71.3)	35 (72.9)	32 (69.6)	
C	11 (11.7)	5 (10.4)	6 (13.0)	
<i>HTR2C</i> , female, % ^a				1.00
Missing	11 (13.7)	6 (14.3)	5 (13.2)	
AA	42 (52.5)	22 (52.3)	20 (52.6)	
AC	23 (28.8)	12 (28.6)	11 (28.9)	
CC	4 (5.0)	2 (4.8)	2 (5.3)	
HTTLRP, %				.32
Missing	26 (14.9)	14 (15.4)	12 (14.2)	
LL	61 (34.9)	35 (38.4)	26 (31.0)	
SL	63 (36.0)	28 (30.8)	35 (41.7)	
SS	25 (14.2)	14 (15.4)	11 (13.1)	
BDNF, %				.16
Missing	27 (15.4)	14 (15.4)	13 (15.5)	
AA	7 (4.0)	6 (6.6)	1 (1.2)	
AG	35 (20.0)	19 (20.9)	16 (19.0)	
GG	106 (60.6)	52 (57.1)	54 (64.3)	
<i>CYP2</i> Genotype				.20
Missing	18 (10.3)	13 (14.3)	5 (6.0)	
Poor/intermediate metabolizer	54 (30.9)	23 (25.3)	31 (36.9)	
Rapid/extensive metabolizer	103 (58.8)	55 (60.4)	48 (57.1)	

Abbreviations: *HTR2A*, serotonin receptor 2A; *HTR2C*, serotonin receptor 2C; *HTT*-LPR, serotonin transporter; BDNF, brain-derived neurotrophic factor; *APOE*-ε4, apolipoprotein E ε4 variant; *CYP2*, cytochrome P450.

^aHTR2C is X-linked.

Table 3

Test for Interactions between Allelotypes and Clinical Outcomes.

	Gene	LR/ χ^2 Test	df	P Value
CMAI	<i>HTR2A</i> (CC vs. CT vs. TT)	1.96	2	.37
	<i>HTR2C</i> (AA vs. AC vs. CC) ^a	0.13	2	.71
	<i>HTTLPR</i> (LL vs. SL vs. SS)	1.99	2	.37
	<i>BDNF</i> (AA vs. GA vs. GG)	0.40	1	.52
	<i>APOE</i> (ϵ 4 vs. no ϵ 4)	0.73	1	.39
	<i>CYP2</i> (Rapid/Extensive vs. Intermediate/Poor)	0.44	1	.50
NBRS Agitation	<i>HTR2A</i> (CC vs. CT vs. TT)	0.22	2	.89
	<i>HTR2C</i> (AA vs. AC vs. CC) ^a	0.50	2	.45
	<i>HTTLPR</i> (LL vs. SL vs. SS)	0.78	2	.68
	<i>BDNF</i> (AA vs. GA vs. GG)	0.30	1	.58
	<i>APOE</i> (ϵ 4 vs. no ϵ 4)	1.55	1	.21
	<i>CYP2</i> (rapid/extensive vs intermediate/poor)	0.01	1	.94
NPI Agitation	<i>HTR2A</i> (CC vs CT vs TT)	6.19	2	.04
	<i>HTR2C</i> (AA vs AC vs CC) ^a	0.27	2	.60
	<i>HTTLPR</i> (LL vs SL vs SS)	0.73	2	.69
	<i>BDNF</i> (AA vs GA vs GG)	1.13	1	.29
	<i>APOE</i> (ϵ 4 vs no ϵ 4)	1.13	1	.29
	<i>CYP2</i> (rapid/extensive vs intermediate/poor)	0.02	1	.92
mADCS-CGIC	<i>HTR2A</i> (CC vs CT vs TT)	0.56	2	.76
	<i>HTR2C</i> (AA vs AC vs CC) ^a	4.33	2	.02
	<i>HTTLPR</i> (LL vs SL vs SS)	0.68	2	.71
	<i>BDNF</i> (AA vs GA vs GG)	0.07	1	.79
	<i>APOE</i> (ϵ 4 vs no ϵ 4)	0.54	1	.46
	<i>CYP2</i> (rapid/extensive vs intermediate/poor)	2.89	1	.09

Abbreviations: DF, degrees of freedom; LR, likelihood ratio; χ^2 , chi-square test for interactions; CMAI, Cohen-Mansfield Agitation Inventory; NBRS, Neurobehavioral Rating Scale; NPI, Neuropsychiatric Inventory; mADCS-CGIC, modified Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; *HTR2A*, serotonin receptor 2A; *HTR2C*, serotonin receptor 2C; *HTT-LPR*, serotonin transporter; *BDNF*, brain-derived neurotropic factor; *APOE*- ϵ 4, apolipoprotein E ϵ 4 variant; *CYP*, cytochrome P450.

^a *HTR2C* is X-linked and sex was adjusted for as a covariate in the model.