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Sertraline for the Treatment of Depression in Alzheimer Disease: Genetic Influences

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Abstract

Objective—To assess the potential for genetic influences on sertraline treatment efficacy for depression of Alzheimer disease (dAD). Four functional genetic variants were studied: 2 serotonin receptors (HTR2A-T102C and HTR2C-Cys23Ser), the serotonin transporter (5HTT-LPR), and brain-derived neurotrophic factor (BDNF-Val66Met). Treatment response by genotype was measured by (1) the modified Alzheimer's Disease Cooperative Study Clinical Global Impression of Change, (2) the Cornell scale for Depression in Dementia, and (3) remission of depression.

Methods—We utilized data from the Depression in Alzheimer's Disease Study 2 (DIADS-2), a 24-week, randomized, multicenter trial showing no significant treatment effect of sertraline on dAD. Proportional odds logistic regression and mixed effects models were used to examine the above mentioned outcome measures.

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Declaration of Conflicting Interests

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Results—No significant interactions were seen between any of the genetic polymorphisms and the selected outcomes above at 12 or 24 weeks.

Discussion—Treatment outcomes in the DIADS-2 trial were not significantly influenced by genetic variation at the loci that were assessed. Future studies should continue to examine the interaction of depression-related genetic variants with antidepressant treatment in Alzheimer disease patients with depression.

Keywords

Alzheimer disease; sertraline; depression; randomized trial; dementia; antidepressant

Objective

As the mean age of the population has increased, there has been a notable increase in the prevalence of dementia and in particular Alzheimer disease (AD) prevalence.[1] Alzheimer disease is marked by progressive neurodegeneration resulting in cognitive deficits. Neuropsychiatric symptoms are almost universal through the course of illness, such as agitation, depression, apathy, delusions/hallucinations, among others.[2,3] Depressive symptoms affect 30% to 50% of individuals with AD.[4] Because depression often appears with an atypical presentation in AD, characterized by more motivational and psychotic symptoms with less guilt, suicidal thoughts, and low self-esteem, many have come to believe that depression in AD (dAD) represents a distinct syndrome.[5,6] Research on the efficacy of several antidepressants for depression in AD has led to conflicting results.[7–12]

The Depression in Alzheimer's Disease Study 2 (DIADS-2) was a randomized, placebo-controlled multicenter trial designed to investigate the efficacy and safety of the selective serotonin reuptake inhibitor (SSRI) sertraline in dAD.[13] In the primary results from the trial's 12-week[14] and 24-week[15] follow-ups, sertraline was not found to be efficacious for the treatment of dAD. A subgroup analysis by Drye et al.[16] that subdivided DIADS-2 participants into those who at the baseline met the criteria for major depressive episode, minor depressive episode, and Alzheimer-associated affective disorder found no efficacy for sertraline in any of these subgroups.

Research focused on the role of genetics in 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 regards to age, the overall effect of genetics, and genetic effects on particular drugs and particular disease processes.[17–26]

In light of this background, we hypothesized that DIADS-2 participants with certain genetic backgrounds might be more likely to respond to sertraline and hence collected DNA on consenting participants. We then conducted genetic analyses on 4 relevant genes for which polymorphisms have been associated with depression or response to antidepressant treatment: 2 serotonin receptors (HTR2A and HTR2C), the serotonin transporter (5HTT), and brain-derived neurotrophic factor (BDNF). Specific allelic variants and polymorphisms of these genes were genotyped. HTR2A-T102C is a single-nucleotide polymorphism that has been associated with psychosis and depression in AD.[21,23] HTR2C-Cys23Ser is an allelic variant known to influence levels of monoamines in the brain, especially nor-epinephrine.[22] 5HTT-LPR is a common functional polymorphism found in the promoter region of the *5HTT* gene that has been associated with the efficacy of antidepressant treatments and faster response time to sertraline in the elderly.[17,18,24] BDNF-Val66Met is a single-nucleotide polymorphism that shows different allelic variations in depressed and

nondepressed individuals.[19,20] Associations between BDNF and AD-related depression[25] and with remission rates in late-life depression[2,6] have also been noted.

In this article, we report on sertraline efficacy in subgroups of participants who were carriers of different alleles. Specifically, we differentiated participants according to the presence/absence and homozygosity/heterozygosity of the HTR2A-T102C, HTR2C-Cys23Ser, 5HTT-LPR, and BDNF-Val66Met variants. We examined treatment response by genotype as measured by (1) the modified Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (mADCS-CGIC), (2) the Cornell scale for Depression in Dementia (CSDD), and (3) remission of depression.

Methods

Study Population

We utilized data from the DIADS-2, a 24-week, randomized, multicenter trial with 2 parallel treatment groups assigned in a 1:1 ratio. The methods and primary results of DIADS-2 have been detailed extensively elsewhere.[13–15,16] The study was conducted under the oversight of a Data Safety Monitoring Board operated by the National Institute of Mental Health (NIMH).

To summarize, study participants were diagnosed with AD utilizing the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision [*DSM-IV-TR*]) criteria[27] and had Mini-Mental State Examination scores[28] of 10 to 26 inclusive. Additionally, participants met the "Olin Criteria" for dAD as defined by a NIMH working group.[6] In a *DSM*-type approach, the Olin Criteria state that 3 (or more) of the following symptoms must be present during the same 2-week period and represent a change from previous functioning: (1) clinically significant depressed mood, (2) decreased positive affect or pleasure in response to social contacts and usual activities, (3) disruption in appetite, (4) disruption in sleep, (5) psychomotor changes, (6) fatigue or loss of energy, (7) feelings of worthlessness, hopelessness, or excessive or inappropriate guilt, (8) diminished ability to think or concentrate, (9) recurrent thoughts of death, suicidal ideation, plan, or attempt, (10) social isolation or withdrawal, and (11) irritability.

Recruitment occurred at 5 academic clinical sites: memory clinics, geriatric psychiatry clinics, Veterans Administration geriatric clinics, community outreach, and Alzheimer's Research Center pools and registries. In accordance with the recommendations of the Alzheimer Association for consent of cognitively impaired adults,[29] consent was obtained from all participants and their legally authorized representative using procedures established by individual sites and their institutional review boards. 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) sertraline (target dose: 100 mg/day) or (2) placebo. During the first 4 weeks postrandomization, clinicians could adjust the dosage of the medication according to patient response and control of side effects. In additional to patient therapy, caregivers were given 20- to 30-minute standardized counseling sessions every 4 weeks, provided with educational materials, and 24-hour access to crisis management assistance. Patients and caregivers followed via in-person visits were seen at baseline, 2, 4, 8, 12, 16, 20, and 24 weeks postrandomization. At 12 weeks, patients without improved scores on the mADCS-CGIC (described below) had the option of being tapered off the study medication and switched to a treatment chosen by their physician. Patients who showed improvement continued with the randomized treatment until week 24. At week 24, 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 Pure-gene Blood Kit from Qiagen (Germantown, Maryland; cat# 158389) and following the manufacturer's protocol. Genotyping was performed by the TaqMan method utilizing the assays on demand (TM) product from Applied Biosystems (Carlsbad, California) with the exception of 5HTT-LPR. The latter was genotyped after polymerase chain reaction amplification with primers GGCGTTGCCGCTCTGAATGC 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. Alleles were called by 2 study investigators.

Outcome Assessment

During the study, patients were assessed with the mADCS-CGIC, which is an adaptation of ADCS-CGIC,[30] that incorporates a global rating of mood symptoms. The mADCS-CGIC is a 7-point Likert scale ranging from 7 = *much worse* to 4 = *no change* to 1 = *much better*. In addition, the CSDD[31] and the Neuropsychiatric Inventory[32] were administered. Remission of depression was defined by a combination of mADCS-CGIC score ≤2 and CSDD score ≤6. Furthermore, at baseline, 8, 16, and 24 weeks, a neurocognitive battery was administered into each participant. The components of this neurocognitive battery have been published previously.[13]

Analysis

All analyses were performed according to each patient's original treatment assignment (intention to treat). The statistical analysis for the overall treatment effect for mADCS-CGIC, CSDD, and remission outcomes have been described in detail previously.[14,15]

The CSDD scores over the 24 weeks were compared using mixed effects models, allowing a random intercept and slope for each patient. The CSDD scores were skewed to the right so a square root transformation of the scores was used as the outcome in regression models. Polynomial terms for time were used to model the trajectory of CSDD overtime in the treatment groups. To test for different rates of change in CSDD over time in the treatment groups and subgroups, a likelihood ratio (LR) test was used to compare a model allowing the changes overtime to differ by treatment groups and subgroup to a model that did not allow the changes over time to differ by treatment group and subgroup by adding interactions for treatment group by time by subgroup.

The comparison of the 2 treatment groups at weeks 12 and 24 of ratings on the mood domain of the mADCS-CGIC was performed with proportional odds logistic regression. The proportion of patients whose depression was remitted at weeks 12 and 24 was compared using logistic regression. Subgroup effects were formally tested in the logistic regression models by adding interaction terms for subgroup-by-treatment group. No adjustments for multiple testing were made.

In general, the subgroup variables were added to the models as unordered categorical variables. However, when exploratory plots and tables indicated the variation in treatment effect across the subgroups had a monotonic trend, tests for trend were also performed.

Statistical analysis and graphs were performed using SAS version 9.2 (2002–2008 by SAS Institute Inc, Cary, North Carolina).

Results

Of the 131 patients involved in the study, 117 (89%) gave consent to provide blood for genetic testing and DNA banking. Of the 117 patients who provided consent, blood was collected and genotyping was performed on 95 (82%). Twenty of the originally consented patients did not ultimately donate blood, and blood samples for 2 patients were lost at the central repository.

Table 1 shows the baseline characteristics of the DIADS-2 patients who provided a DNA sample and thus were included in the study. No statistically significant differences (defined as $P \leq .05$) existed between the treatment and control group on these baseline characteristics. Patients who agreed to provide blood for DNA were similar to patients who refused to provide blood for DNA with respect to most baseline demographic and clinical characteristics. This includes no significant differences in concomitant medication use (82.6% of placebo group vs 75.5% of sertraline group were on other AD medications and 23.9% of placebo vs 28.6% of sertraline were on medications other than AD medications). However, the mean baseline CSDD score was lower (indicating less depression) in patients who provided DNA versus those who did not (12.8 [5.3] vs 16.2 [5.9]; $P = .004$), and the proportion of patients who were African American was lower in the group that provided DNA versus the group that did not (17% vs 33%; $P = .01$).

Table 2 compares gene distribution between the sertraline and placebo groups. No significant differences were seen between the groups for any of the polymorphisms analyzed: HTR2A-T102C, HTR2C-Cys23Ser, 5HTT-LPR, and BDNF-Val66Met.

Table 3 shows the resulting LR, chi-square (χ^2) statistics for test of interactions analyses for each of the genetic polymorphisms analyzed. No significant interactions were seen between any of the genetic polymorphisms and the selected outcome measures: mADCS-CGIC, CSDD, and remission of depression at 12 or 24 weeks.

The *HTR2A* allele variants exhibited a monotonic pattern in the treatment effect for the CSDD, mADCS-CGIC, and remission outcomes. The magnitude of the treatment effect (sertraline vs placebo) decreased like effect in TT > effect in CT > effect in CC. However, tests for trend were not significant for any of the outcomes (data not shown).

Note that since allele frequencies may differ by ethnic group, we considered ethnic group to be a potential confounder and performed sensitivity analyses for the remission outcome controlling for ethnicity. The coefficient estimates and standard errors for the allele by treatment group interactions were very similar in models with and without control for ethnicity giving no evidence that the null finding is due to confounding by ethnicity.

Discussion

The results of the present study, although limited by a small sample size, showed no significant interaction between treatment response to sertraline in dAD and known allelic variants and polymorphisms in 2 serotonin receptors (HTR2A and HTR2C), the serotonin transporter (5HTT), and BDNF. Using 3 outcome measures (mADCS-CGIC, CSDD, and remission of depression), we have previously reported null results at 12 weeks and[14] 24 weeks[15] and stratified by major or minor depression diagnosis.[16] The present study reports that this general lack of treatment effect does not differ considerably among carriers of different alleles at these loci, which were chosen for their possible associations with mood disorder diagnoses and treatment response.

Strengths/Limitations

Strengths of this study include (1) randomized treatment assignment with inclusion of placebo control group, (2) double-blind treatment assignments with rigorous adherence to masked rating, (3) high retention rates and a high rate of adherence to study drug, (4) use of a consensus definition of depression of AD, (5) use of a semistructured psychosocial intervention in a multicenter trial with centralized training and monitoring of adherence to the protocol, and (6) relatively few medical or medication exclusions resulting in a study population that is broadly a representative of the population with AD.

Limitations of the study include (1) participants comprised a sample of convenience in US academic medical centers and hence may not generalize to other settings, (2) small sample size of individuals providing DNA sample leading to reduced power to detect potential small effects of genotype on treatment response, (3) lack of stratification by ApoE genotype because of limited sample size, and (4) lack of analysis of other known associated allelic variants, including those in the genes of the cytochrome enzymes.[33]

Conclusions/Future

This study adds to the existing literature on the use of antidepressants in dAD as well as to the null status of the DIADS-2 study. Studies such as the present that examine genetic influences on treatment response (pharmacogenomics) are increasingly utilized in both general and specialty populations with the hope that pharmacogenomic 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.[34] Future studies should continue to examine treatment effects of antidepressants in larger populations. In addition, analysis of other genetic variants associated with sertraline response is warranted.

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Table 1

Baseline Characteristics of Depression in Alzheimer's Disease Study 2 Patients Who Provided DNA Sample

Characteristics	Sertraline (n = 49)	Placebo (n = 46)	Overall (n = 95)	*P* Value
Age, years				.8714
Mean	77.0	77.3	77.2	
First/third quartile	72.0/83.0	73.0/83.0	72.0/83.0	
Range	57.0–96.0	53.0–92.0	53.0–96.0	
Sex, %				.3688
Male	40.8	50.0	45.3	
Female	59.2	50.0	54.7	
Ethnicity/race, %				.4058
African American	16.3	17.4	16.8	
White, non-Hispanic	73.5	63.0	68.4	
Hispanic/Latino	10.2	19.6	14.7	
Marital status, %				.8777
Married	67.3	67.4	67.4	
Widowed	24.5	21.7	23.2	
Separated	8.2	10.9	9.5	
Education, years				.1408
Mean	13.1	12.0	12.6	
First/third quartile	12.0/16.0	10.0/14.0	11.0/15.0	
Range	3.0–24.0	3.0–18.0	3.0–24.0	
Dementia duration				.0828
Mean	2.4	3.3	2.8	
First/third quartile	1.0/3.0	1.0/4.0	1.0/4.0	
Range	0.0–1.0	0.0–11.0	0.0–11.0	
Depression[a] episodes before cognitive symptoms, %				.2480
Missing	4.1	–	2.1	
No episode	81.6	71.7	76.8	
One episode	8.2	17.4	12.6	
Two episodes	4.1	2.2	3.2	
≥3 Episodes	2.0	8.7	5.3	
Depression[a] episodes after cognitive symptoms, %				.7805
Missing	2.0	–	1.1	
One episode	87.8	84.8	86.3	
Two episodes	6.1	8.7	7.4	
≥3 Episodes	4.1	6.5	5.3	
MMSE				.0555
Mean	20.8	18.9	19.9	
First/third quartile	17.0/25.0	14.0/24.0	16.0/24.0	
Range	11.0–28.0	10.0–27.0	10.0–28.0	
CSDD				.9377

Characteristics	Sertraline (n = 49)	Placebo (n = 46)	Overall (n = 95)	*P* Value
Mean	12.9	12.7	12.8	
First/third quartile	9.0/17.0	9.0/16.0	9.0/17.0	
Range	4.0–25.0	4.0–22.0	4.0–25.0	

Abbreviations: MMSE, Mini-Mental State Examination; CSDD, Cornell scale for Depression in Dementia.

[a]Major Depressive Episode.

Table 2

Gene Distribution Among 2 Treatment Groups

Characteristics	Sertraline (n = 49)	Placebo (n = 46)	Overall (n = 95)	*P* Value
HTR2A, %				.3440
Missing	0	4.3	2.1	
CC	34.7	30.4	32.6	
CT	46.9	56.5	51.6	
TT	18.4	8.7	13.7	
HTR2C, %				.8949
AA	65.3	69.6	67.4	
AC	18.4	15.2	16.8	
CC	16.3	15.2	15.8	
HTT-LPR, %				.9395
LL	34.7	37.0	35.8	
SL	44.9	41.3	43.2	
SS	20.4	21.7	21.1	
BDNF, %				.3732
AA	0	2.2	1.1	
GA	26.5	34.8	30.5	
GG	63.5	63.0	68.4	

Table 3

Subgroup Analyses by Outcome—Test for Interactions

	Subgroup	LR/χ^2 Test	DF	*P* Value
mADCS-CGIC (week 12)	HTR2A (CC vs CT vs TT)	0.16	2	.92
	HTR2C (AA vs AC vs CC)	3.47	2	.18
	HTT-LPR (LL vs SL vs SS)	0.71	2	.70
	BDNF (GA vs GG)	0.82	1	.36
mADCS-CGIC (week 24)	HTR2A (CC vs CT vs TT)	1.58	2	.45
	HTR2C (AA vs AC vs CC)	1.23	2	.54
	HTT-LPR (LL vs SL vs SS)	3.01	2	.22
	BDNF (GA vs GG)	0.76	1	.38
CSDD (week 12)	HTR2A (CC vs CT vs TT)	5.28	4	.26
	HTR2C (AA vs AC vs CC)	5.61	4	.23
	HTT-LPR (LL vs SL vs SS)	1.32	4	.86
	BDNF (GA vs GG)	1.42	2	.49
CSDD (over week 24)	HTR2A (CC vs CT vs TT)	7.21	4	.12
	HTR2C (AA vs AC vs CC)	1.70	4	.79
	HTT-LPR (LL vs SL vs SS)	7.19	4	.13
	BDNF (GA vs GG)	2.74	2	.25
Remission[a] (week 12)	HTR2A (CC vs CT vs TT)	0.10	2	.95
	HTR2C (AA vs AC vs CC)	0.95	2	.62
	HTT-LPR (LL vs SL vs SS)	0.83	2	.66
	BDNF (GA vs GG)	0.14	1	.70
Remission[a] (week 24)	HTR2A (CC vs CT vs TT)	0.48	2	.78
	HTR2C (AA vs AC vs CC)	1.42	2	.49
	HTT-LPR (LL vs SL vs SS)	0.33	2	.85
	BDNF (GA vs GG)	0.09	1	.77

Abbreviations: DF, degrees of freedom; LR, Likelihood ratio; χ^2, chi-square test for interactions; mADCS-CGIC, modified Alzheimer's Disease Cooperative Study Clinical Global Impression of Change index; CSDD, Cornell Scale for Depression in Dementia.

[a]Remission of depression defined as a combination of mADCS-CGIC score <2 and CSDD score <6.