Original Investigation

Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia
A Randomized Clinical Trial

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IMPORTANCE Agitation is common among patients with Alzheimer disease; safe, effective treatments are lacking.

OBJECTIVE To assess the efficacy, safety, and tolerability of dextromethorphan hydrobromide–quinidine sulfate for Alzheimer disease–related agitation.

DESIGN, SETTING, AND PARTICIPANTS Phase 2 randomized, multicenter, double-blind, placebo-controlled trial using a sequential parallel comparison design with 2 consecutive 5-week treatment stages conducted August 2012–August 2014. Patients with probable Alzheimer disease, clinically significant agitation (Clinical Global Impressions–Severity agitation score ≥4), and a Mini-Mental State Examination score of 8 to 28 participated at 42 US study sites. Stable dosages of antidepressants, antipsychotics, hypnotics, and antidementia medications were allowed.

INTERVENTIONS In stage 1, 220 patients were randomized in a 3:4 ratio to receive dextromethorphan-quinidine (n = 93) or placebo (n = 127). In stage 2, patients receiving dextromethorphan-quinidine continued; those receiving placebo were stratified by response and rerandomized in a 1:1 ratio to dextromethorphan-quinidine (n = 59) or placebo (n = 60).

MAIN OUTCOMES AND MEASURES The primary end point was change from baseline on the Neuropsychiatric Inventory (NPI) Agitation/Aggression domain (scale range, 0 [absence of symptoms] to 12 [symptoms occur daily and with marked severity]).

RESULTS A total of 194 patients (88.2%) completed the study. With the sequential parallel comparison design, 152 patients received dextromethorphan-quinidine and 127 received placebo during the study. Analysis combining stages 1 (all patients) and 2 (rerandomized placebo nonresponders) showed significantly reduced NPI Agitation/Aggression scores for dextromethorphan-quinidine vs placebo (ordinary least squares *z* statistic, −3.95; $P < .001$). In stage 1, mean NPI Agitation/Aggression scores were reduced from 7.1 to 3.8 with dextromethorphan-quinidine and from 7.0 to 5.3 with placebo. Between-group treatment differences were significant in stage 1 (least squares mean, −1.5; 95% CI, −2.3 to −0.7; $P<.001$). In stage 2, NPI Agitation/Aggression scores were reduced from 5.8 to 3.8 with dextromethorphan-quinidine and from 6.7 to 5.8 with placebo. Between-group treatment differences were also significant in stage 2 (least squares mean, −1.6; 95% CI, −2.9 to −0.3; $P=.02$). Adverse events included falls (8.6% for dextromethorphan-quinidine vs 3.9% for placebo), diarrhea (5.9% vs 3.1% respectively), and urinary tract infection (5.3% vs 3.9% respectively). Serious adverse events occurred in 7.9% with dextromethorphan-quinidine vs 4.7% with placebo. Dextromethorphan-quinidine was not associated with cognitive impairment, sedation, or clinically significant QTc prolongation.

CONCLUSIONS AND RELEVANCE In this preliminary 10-week phase 2 randomized clinical trial of patients with probable Alzheimer disease, combination dextromethorphan-quinidine demonstrated clinically relevant efficacy for agitation and was generally well tolerated.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01584440

JAMA. 2015;314(12):1242-1254. doi:10.1001/jama.2015.10214

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Agitation and aggression are highly prevalent in patients with dementia[1,2] and are associated with distress for patients and caregivers, greater risk of institutionalization, and accelerated progression to severe dementia and death.[3-5] Nonpharmacological interventions are recommended as first-line therapy, but many patients fail to respond, and pharmacotherapy is often needed.[5-7] Although many classes of psychotropic drugs are prescribed for agitation, safety concerns and modest or unproven efficacy limit their utility. Antipsychotics have shown benefit for Alzheimer disease–related psychosis, but their use is associated with excess mortality, cerebrovascular events, sedation, falls, cognitive impairment, metabolic syndrome, parkinsonism, and tardive dyskinesia.[5,8] A recent trial showed that citalopram, a selective serotonin reuptake inhibitor, was associated with improvement in agitation in Alzheimer disease but was associated with prolonged QTc interval and mild cognitive decline.[9] Safe and effective therapies targeting Alzheimer disease–related agitation are needed.[5]

CGIS *Clinical Global Impressions–Severity*

MMSE *Mini-Mental State Examination*

NPI *Neuropsychiatric Inventory*

QTcF *Fridericia-corrected QT interval*

The combination of dextromethorphan hydrobromide and quinidine sulfate is approved for the treatment of pseudobulbar affect in the United States and European Union. Dextromethorphan is a low-affinity, uncompetitive *N*-methyl-D-aspartate receptor antagonist,[10] σ_1 receptor agonist,[11] serotonin and norepinephrine reuptake inhibitor,[12] and neuronal nicotinic $\alpha_3\beta_4$ receptor antagonist.[13] Evidence suggesting a potential effect of dextromethorphan-quinidine for agitation comes from controlled clinical trial data in nondemented patients with pseudobulbar affect,[14] published case descriptions,[15] and anecdotal reports of improvement in patients with dementia, pseudobulbar affect, and symptoms suggestive of agitation.

Herein we report the results of a randomized clinical trial to assess the efficacy and safety of dextromethorphan-quinidine for moderate to severe agitation associated with Alzheimer disease.

Methods

Trial Design and Setting

This randomized, double-blind, placebo-controlled, 10-week trial was conducted at 42 US sites including outpatient Alzheimer disease clinics and assisted living and nursing facilities. This clinical trial was conducted using the Trimentum (Pharmaco Investments Inc) sequential parallel comparison design method, under license from PPD Development LP, consisting of 2 consecutive 5-week stages to enhance the ability to detect a treatment signal even in the context of a robust placebo response (eFigure in Supplement 1).[16] An independent data and safety monitoring board oversaw the study, and institutional review boards at each site approved the study protocol and its amendments (see Supplement 2 for trial protocol and Supplement 3 for statistical analysis plan). All patients or authorized representatives or caregivers provided written informed consent.

Participants

Eligible patients were aged 50 to 90 years with probable Alzheimer disease (based on 2011 National Institute on Aging–Alzheimer Association criteria) and clinically significant agitation, defined as a state of poorly organized and purposeless psychomotor activity characterized by at least 1 of the following: aggressive verbal (eg, screaming, cursing), aggressive physical (eg, destroying objects, grabbing, fighting), or nonaggressive physical (eg, pacing, restlessness) behaviors.[17] Eligible patients had behavioral symptoms that interfered with daily routine, were severe enough to warrant pharmacological treatment, scored 4 or higher (moderately ill) on the Clinical Global Impressions–Severity (CGIS) scale for agitation,[18] and had a Mini-Mental State Examination (MMSE) score of 8 to 28. Stable dosages of Alzheimer disease medications (≥2 months; memantine and/or acetylcholinesterase inhibitors) and specified antidepressants, antipsychotics, or hypnotics (≥1 month; including short-acting benzodiazepines and nonbenzodiazepines) were allowed; dosages were to remain stable throughout the study.

Exclusion criteria were non–Alzheimer disease dementia; agitation not secondary to Alzheimer disease; hospitalization in a mental health care facility; significant depression (Cornell Scale for Depression in Dementia score ≥10); schizophrenia or schizoaffective or bipolar disorder; myasthenia gravis (because quinidine use is contraindicated); clinically significant/unstable systemic disease; history of complete heart block, QTc prolongation, or torsades de pointes; family history of congenital QT prolongation; history of postural or unexplained syncope within the last year; or substance/alcohol abuse within 3 years. First-generation antipsychotics and tricyclic and monoamine oxidase inhibitor antidepressants were not allowed.

Race and ethnicity were self-reported or provided by a knowledgeable informant based on categories defined by the US Food and Drug Administration (FDA) Guidance for Industry for Collection of Race and Ethnicity Data in Clinical Trials.

Interventions

In stage 1, patients were randomized 3:4 to receive oral administration of dextromethorphan-quinidine or matching placebo. Dextromethorphan-quinidine was dosed as 20/10 mg once daily in the morning (with placebo in the evening) for week 1. Dextromethorphan-quinidine was increased to twice daily for weeks 2 and 3 and then increased to 30/10 mg twice daily for weeks 4 and 5. In stage 2, patients receiving dextromethorphan-quinidine continued to receive 30/10 mg twice daily. Patients who received placebo during stage 1 were stratified by treatment response and rerandomized in a 1:1 ratio to receive dextromethorphan-quinidine (dosage escalated as described above) or matching placebo. Patients were considered responders at the end of stage 1 if their CGIS score for agitation was 3 (mildly ill) or lower and their Neuropsychi-

atric Inventory (NPI) Agitation/Aggression domain score decreased by 25% or more from baseline.

Oral lorazepam (maximum dosage of 1.5 mg/d and maximum of 3 days in a 7-day period) was allowed as rescue medication for agitation if deemed necessary by the study investigator.

Outcomes

The prespecified primary efficacy end point was change from baseline in the NPI Agitation/Aggression domain. Each NPI domain was rated by the caregiver for symptom frequency (1-4: occasionally [less than once per week], often [about once per week], frequently [several times per week], or very frequently [once or more per day], respectively) and severity (1-3: mild, moderate, or marked, respectively); a score of 0 indicated no symptoms. The NPI's scoring yields a composite (frequency × severity) score of 1 to 12 for each positively endorsed domain.

Secondary efficacy end points included changes from baseline in NPI total score (range, 0-144), individual NPI domain scores, and NPI composite scores comprising the Agitation/Aggression, Aberrant Motor Behavior, and Irritability/Lability domains plus either the Anxiety domain (NPI4A) or the Disinhibition domain (NPI4D). An NPI Caregiver Distress score for each positively endorsed NPI domain captured how emotionally distressing the caregiver found the behavior (range, 0-5; not at all to very severely or extremely). Alzheimer Disease Cooperative Study (ADCS) Clinical Global Impression of Change scores (range, 1-7; marked improvement to marked worsening) and Patient Global Impression of Change scores, rated by a caregiver (range, 1-7; very much improved to very much worse), were assessed at weeks 5 and 10 and provided measures of clinical meaningfulness. Additional secondary end points included the ADCS Activities of Daily Living Inventory (range, 0-54; higher scores signifying better function); Cornell Scale for Depression in Dementia (range, 0-38; higher scores signifying more severe depression); Caregiver Strain Index (range, 0-13; higher scores signifying higher stress levels); Quality of Life–Alzheimer Disease score (range, 13-52; higher scores signifying better quality of life); and psychotropic medication changes/rescue use of lorazepam. Cognition was assessed using the MMSE (range, 0-30; lower scores signifying greater cognitive impairment) and the Alzheimer Disease Assessment Scale–Cognitive Subscale (range, 0-70; higher scores signifying greater cognitive impairment). Safety outcomes included adverse events, vital signs, clinical laboratory test results, and electrocardiographic findings. Results for QT interval were corrected for variation in heart rate and calculated according to the formula of Fridericia (QTcF): $(QT/\sqrt[3]{[RR]})$.[19]

Sample Size Calculation

In published treatment studies for dementia-related agitation, standard deviation estimates for change in NPI Agitation/Aggression scores range from 3.1 to 5.2 points.[20-22] Assuming an SD of 5.0 points and based on a 2-sided, 2-sample comparison of means from independent samples at the .05 significance level, a sample size of 196 patients would provide 90% power to detect a mean difference of 2.5 points. The sample size calculation was based on a parallel design because there was no precedent for a sequential parallel comparison design trial of agitation in Alzheimer disease.

Randomization

The randomization scheme was designed by the sponsor and managed by the contract research organization using an interactive Web response system. The randomization in stage 1 was stratified by baseline cognitive function (MMSE score of >15 vs ≤15) and agitation severity (CGIS score of 4-5 vs 6-7); blocked randomization ensured treatment balance in each stratum.

Masking

Dextromethorphan-quinidine and placebo capsules were identical in appearance. The sponsor, patients, caregivers, and investigators were unaware of treatment assignment. All study sites, patients, and caregivers were blinded to the use of sequential parallel comparison design and unaware of the responder criteria and midstudy rerandomization.

Statistical Analysis

The safety analysis set included all patients who took at least 1 dose of study medication. The modified intention-to-treat analysis set for efficacy included all patients with a postbaseline NPI Agitation/Aggression assessment in stage 1. In primary analysis, missing data were imputed using last observation carried forward; in sensitivity analysis, missing data were handled using a mixed-effects model assuming a missing-at-random mechanism.

Primary and secondary efficacy end points were analyzed based on published sequential parallel comparison design methods[16,23] analyzing data from both 5-week stages with 1:1 weighting using ordinary least squares and including all patients in stage 1 and only the rerandomized placebo nonresponders in stage 2. The primary study end-point analysis was prespecified; no correction was performed to address multiplicity in the secondary end points. Dextromethorphan-quinidine and placebo groups were compared using 2-sided tests at the $\alpha = .05$ level of significance. Additionally, analysis of covariance with treatment as the fixed effect and baseline as the covariate was used to compare treatment group means at each stage and visit, separately. To simulate a 10-week parallel-group design, we also conducted a prespecified comparison of NPI Agitation/Aggression scores between patients who were randomized to receive only dextromethorphan-quinidine vs only placebo for the entire 10 weeks of the trial (regardless of responder status). All statistical analyses were performed using SAS version 9.1 or higher (SAS Institute Inc).

Given the use of sequential parallel comparison design methods and to ensure findings from the primary analysis, additional exploratory sensitivity analyses of the primary end point were carried out. One used the repeated-measures model (prespecified) described by Doros et al[24] to test the potential statistical effect of missing data and the exclusion of rerandomized placebo "responders" in stage 2. This model uses all

available data from the NPI Agitation/Aggression domain. Three separate models were used to estimate treatment effect and included data collected at baseline, end of stage 1, and end of stage 2, with a general model that allows inclusion of data from intermediate visits. Based on an FDA recommendation, the second sensitivity analysis of the primary end point, using the seemingly unrelated regression method[24-26] in the sequential parallel comparison design instead of the ordinary least squares method, was conducted after unblinding of the study to address whether missing data could be missing not at random. In addition, a prespecified exploratory analysis of the primary end point was carried out that used the same sequential parallel comparison design method described above for the primary analysis but including both placebo responders and nonresponders who were rerandomized in stage 2.

Results

Patients

Patients were recruited between July 23, 2012, and May 22, 2014; the last patient completed the study on July 31, 2014, and the study closed August 30, 2014, at expiration of the 30-day safety reporting window. All 220 randomized patients (126 women and 94 men) were included in the safety analysis set; 218 patients comprised the modified intention-to-treat analysis set for efficacy, and 194 (88.2%) completed the study (**Figure 1**). With the sequential parallel comparison design and rerandomization of the placebo group on entry into stage 2, a total of 152 patients received dextromethorphan-quinidine (93 starting from stage 1 and an additional 59 rerandomized from the placebo group in stage 2) and 127 patients received placebo, resulting in an approximately 26.7% greater exposure to dextromethorphan-quinidine (1153 patient-weeks) than to placebo (911 patient-weeks). Seventeen patients (11.2%) discontinued the study while receiving dextromethorphan-quinidine and 9 (7.1%) while receiving placebo, including 8 (5.3%) and 4 (3.1%) for adverse events, respectively. Patient characteristics were well balanced across treatment groups (**Table 1**).

Efficacy Outcomes

Primary End Point

Dextromethorphan-quinidine significantly improved the NPI Agitation/Aggression score compared with placebo in the primary sequential parallel comparison design analysis (ordinary least squares z statistic, −3.95; $P < .001$). Results for each stage also favored dextromethorphan-quinidine over placebo (**Table 2**). In stage 1, mean NPI Agitation/Aggression scores were reduced from 7.1 (SD, 2.6) to 3.8 (SD, 3.3) with dextromethorphan-quinidine and from 7.0 (SD, 2.4) to 5.3 (SD, 3.2) with placebo, with a least squares mean treatment difference of −1.5 (95% CI, −2.3 to −0.7; $P < .001$). Differential response was noted by week 1 (least squares mean, −0.8; 95% CI, −1.5 to −0.03; $P = .04$) (**Figure 2**A). In stage 2 (placebo nonresponders rerandomized to either dextromethorphan-quinidine or placebo), mean NPI Agitation/Aggression scores were reduced from 5.8 (SD, 3.0) to 3.8 (SD, 3.1) with dextromethorphan-quinidine and from 6.7 (SD, 2.8) to 5.8 (SD, 3.8) with placebo, with a least squares mean treatment difference of −1.6 (95% CI, −2.9 to −0.3; $P = .02$) (Figure 2B). The prespecified comparison of NPI Agitation/Aggression scores between patients who were randomized to receive only dextromethorphan-quinidine (n = 93) vs only placebo (n = 66) for the entire 10 weeks of the trial (regardless of responder status, simulating a parallel-group design) also favored dextromethorphan-quinidine over placebo (least squares mean treatment difference, −1.8; 95% CI, −2.8 to −0.7; $P = .003$) (Table 2 and Figure 2C). Response to dextromethorphan-quinidine compared with placebo did not appear to differ by disease stage. The stratified randomization by baseline MMSE score (>15 vs ≤15) and baseline CGIS score (4 or 5 vs 6 or 7) resulted in balanced treatment groups for both agitation and cognitive function. Supplemental analyses conducted to assess the potential influence of these factors did not suggest a difference in response.

The repeated-measures model and seemingly unrelated regression sensitivity analyses of the primary end point corroborated the statistical significance observed in the primary efficacy analysis (eTable in Supplement 1). The additional prespecified analysis that included both placebo responders and nonresponders who were rerandomized in stage 2 did not alter the significance or magnitude of effect of the primary analysis.

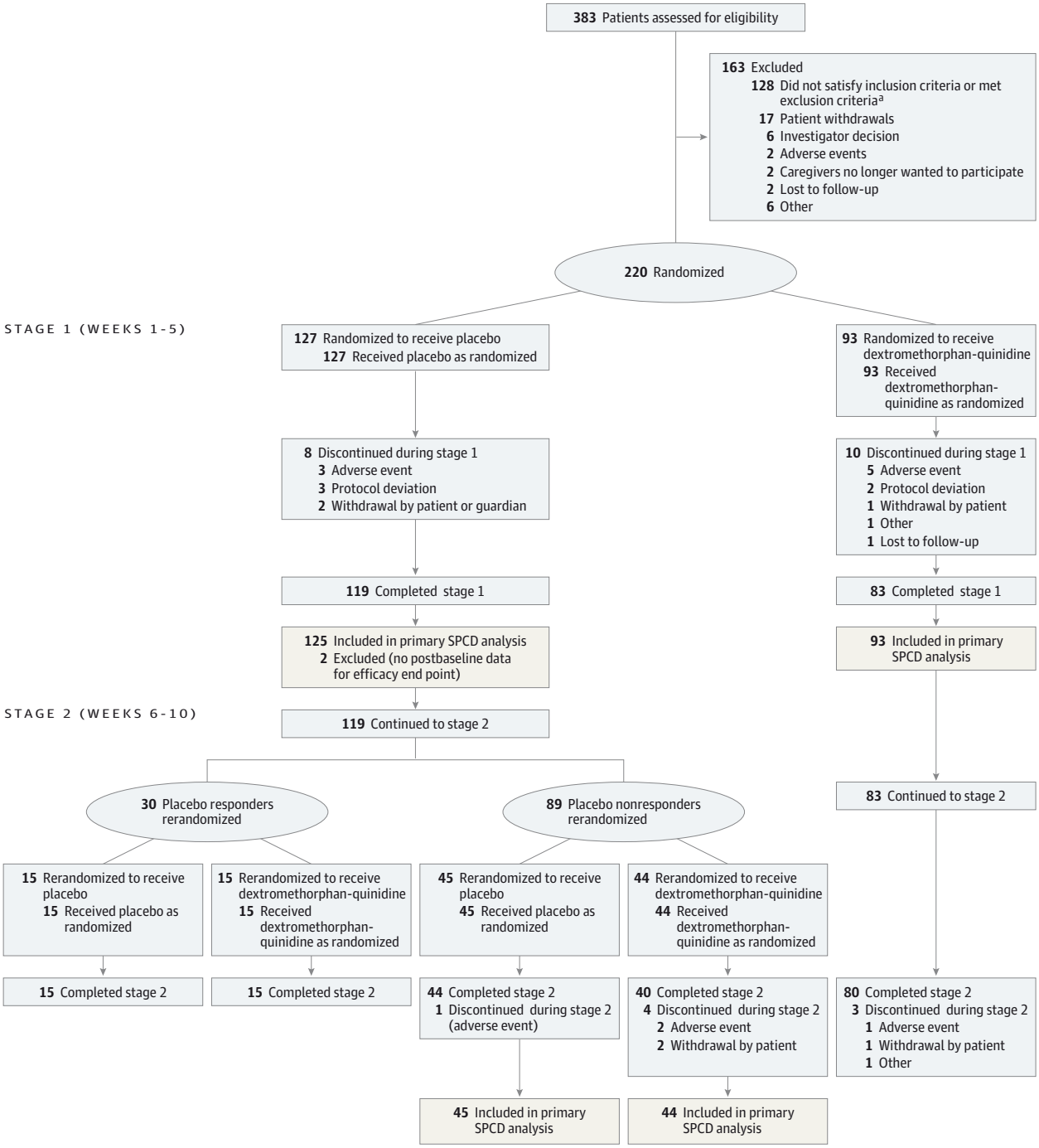
Secondary Outcomes

Sequential parallel comparison design analysis of prespecified secondary outcomes (Table 2 and **Table 3**) showed significant improvement favoring dextromethorphan-quinidine on global rating scores (Patient Global Impression of Change and ADCS Clinical Global Impression of Change), NPI total, NPI Aberrant Motor Behavior domain, NPI Irritability/Lability domain, NPI4A and NPI4D domain composites, NPI Caregiver Distress (as related to both the NPI Agitation/Aggression domain score and NPI total score), Caregiver Strain Index, and Cornell Scale for Depression in Dementia. Results for changes in the Quality of Life-Alzheimer Disease score, ADCS Activities of Daily Living Inventory, MMSE, and Alzheimer Disease Assessment Scale-Cognitive Subscale (an exploratory outcome) were not significant vs placebo. Post hoc analyses showed similar improvement in NPI Agitation/Aggression scores with dextromethorphan-quinidine in patients taking concomitant acetylcholinesterase inhibitors, memantine, antidepressants, or antipsychotics compared with those not receiving these agents. Lorazepam rescue medication was used by 10 of 152 patients (6.6%) during treament with dextromethorphan-quinidine and by 13 of 125 patients (10.4%) during treatment with placebo.

Safety and Tolerability

Treatment-emergent adverse events were attributed based on treatment assignment at the time of occurrence. Treatment-emergent adverse events were reported by 93 of 152 patients (61.2%) and 55 of 127 patients (43.3%) (safety set) during treatment with dextromethorphan-quinidine or

Figure 1. Participant Flow in a Trial of Dextromethorphan-Quinidine for Alzheimer Disease–Related Agitation



SPCD indicates sequential parallel comparison design. The modified intention-to-treat population included 218 patients (placebo, n = 125; dextromethorphan-quinidine, n = 93). At the end of stage 1, response for placebo group stratification was defined as having a Clinical Global Impressions–Severity (CGIS) score for agitation of 3 or lower (mildly ill) and a Neuropsychiatric Inventory Agitation/Aggression domain score decrease of 25% or more from baseline.

[a] Most common reasons for exclusions related to inclusion or exclusion criteria were not having a Mini-Mental State Examinination score between 8 and 28, inclusive (n=26); not having a CGIS score for agitation of at least 4 (n=25); having a personal history of complete heart block, QTc prolongation, or torsade de pointes (n=21); having coexistent clinically significant or unstable systematic disease (n=18); taking a disallowed medication (n=5); and taking an allowed medication but at an unstable dose or duration (n=5).

placebo, respectively. The most commonly occurring treatment-emergent adverse events (>3% and greater than placebo) were falls (8.6% vs 3.9%), diarrhea (5.9% vs 3.1%), urinary tract infection (5.3% vs 3.9%), and dizziness (4.6% vs 2.4%) for dextromethorphan-quinidine vs placebo, respectively. Serious adverse events occurred in 12 patients

Table 1. Baseline Demographic and Clinical Characteristics[a]

Characteristics	Dextromethorphan-Quinidine (n = 93)[b]	Placebo (n = 127)[b]
Age, mean (SD), y	77.8 (8.0)	77.8 (7.2)
Age ≥75 y	68 (73.1)	86 (67.7)
Women	52 (55.9)	74 (58.3)
Race		
White	84 (90.3)	118 (92.9)
Black or African American	5 (5.4)	6 (4.7)
Asian	3 (3.2)	1 (0.8)
Native Hawaiian or other Pacific Islander	1 (1.1)	0
Other	0	2 (1.6)
Ethnicity		
Hispanic or Latino	7 (7.5)	13 (10.2)
Residence		
Outpatient	82 (88.2)	111 (87.4)
Assisted living	5 (5.4)	10 (7.9)
Nursing home	6 (6.5)	6 (4.7)
Concomitant medications		
Acetylcholinesterase inhibitors	67 (72.0)	95 (74.8)
Memantine	43 (46.2)	66 (52.0)
Antidepressants	57 (61.3)	65 (51.2)
Antipsychotics	16 (17.2)	29 (22.8)
Benzodiazepines	6 (6.5)	12 (9.5)
Benzodiazepine-like derivatives	6 (6.5)	12 (9.5)
History of falls	16 (17.2)	16 (12.6)
Rating scale scores, mean (SD)[c]		
Clinical Global Impressions-Severity score for agitation	4.4 (0.6)	4.5 (0.7)
No. (%) with score		
4 (moderately ill)	61 (65.6)	77 (61.6)
5 (markedly ill)	28 (30.1)	38 (30.4)
6 or 7 (severely ill or among the most extremely ill patient)	4 (4.3)	10 (8.0)
Neuropsychiatric Inventory		
Agitation/Aggression domain	7.1 (2.6)	7.0 (2.4)
Total score	40.1 (19.6)	38.0 (18.7)
Aberrant Motor Behavior domain[d]	4.0 (0-8)	2.0 (0-6)
Irritability/Lability domain	5.8 (3.7)	5.4 (3.2)
NPI4A composite	20.9 (9.4)	20.1 (8.3)
NPI4D composite	19.8 (9.1)	18.5 (9.2)
Caregiver distress		
Agitation	3.3 (0.9)	3.0 (1.0)
Total score	17.9 (8.0)	17.0 (8.3)
Caregiver Strain Index	6.9 (3.2)	6.8 (3.6)
Cornell Scale for Depression in Dementia	5.9 (2.4)	5.8 (2.4)
Quality of Life-Alzheimer Disease scale		
Patient	36.5 (7.4)	37.2 (6.4)
Caregiver	30.9 (6.0)	30.1 (6.0)
Mini-Mental State Examination	17.4 (6.0)	17.2 (5.8)
Alzheimer Disease Assessment Scale-Cognitive Subscale	30.6 (14.1)	32.0 (15.2)
Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory	35.8 (11.9)	34.1 (12.8)

Abbreviations: NPI4A, the sum of Neuropsychiatric Inventory Agitation/Aggression, Irritability/Lability, Aberrant Motor Behavior, and Anxiety domain scores; NPI4D, the sum of Neuropsychiatric Inventory Agitation/Aggression, Irritability/Lability, Aberrant Motor Behavior, and Disinhibition domain scores.

[a] Data are expressed as No. (%) of participants unless otherwise indicated.

[b] Safety analysis set at randomization.

[c] Modified intention-to-treat analysis set for efficacy analysis (dextromethorphan-quinidine, n = 93; placebo, n = 125) at stage 1 baseline.

[d] Presented as median (interquartile range). At baseline, the mean Neuropsychiatric Inventory Aberrant Motor Behavior domain scores were 4.3 (SD, 4.4) for dextromethorphan-quinidine and 3.5 (SD, 4.2) for placebo.

(7.9%) receiving dextromethorphan-quinidine and in 6 (4.7%) receiving placebo. Serious adverse events in patients receiving dextromethorphan-quinidine included chest pain (n = 2), anemia, acute myocardial infarction (occurring 2 days after dosing ended), bradycardia, kidney infection, femur fracture, dehydration, colon cancer, cerebrovascular

Table 2. Summary of Efficacy Outcome Measures in the Modified Intention-to-Treat Population

Outcome Measure and Study Stage[a]	No. of Participants		Change From Baseline, Mean (95% CI)		*P* Value by Stage[b]	Least Squares Mean Treatment Difference (95% CI)[c]	*P* Value by SPCD[b,d]
	Dextromethorphan-Quinidine	Placebo	Dextromethorphan-Quinidine	Placebo			
NPI Agitation/Aggression domain[e]							
Stage 1[a]	93	125	−3.3 (−3.9 to −2.6)	−1.7 (−2.3 to −1.2)	<.001	−1.5 (−2.3 to −0.7)	<.001
Stage 2[a]	44	45	−2.0 (−3.0 to −1.0)	−0.8 (−1.9 to 0.2)	.02	−1.6 (−2.9 to −0.3)	
10 wk[f]	93	66	−3.6 (−4.3 to −2.9)	−1.9 (−2.8 to −1.0)	.001	−1.8 (−2.8 to −0.7)	.003
NPI total score[e]							
Stage 1[a]	93	125	−13.5 (−17.1 to −9.9)	−8.5 (−11.0 to −5.9)	.03	−4.2 (−8.0 to −0.4)	.01
Stage 2[a]	44	45	−6.0 (−9.7 to −2.2)	−2.5 (−6.0 to 1.1)	.15	−3.8 (−9.0 to 1.4)	
10 wk[f]	93	66	−16.0 (−19.5 to −12.5)	−10.1 (−14.7 to −5.5)	.02	−5.7 (−10.7 to −0.7)	NA
NPI Aberrant Motor Behavior domain[e]							
Stage 1[a]	93	125	−1.2 (−2.0 to −0.4)	−0.4 (−1.1 to 0.3)	.39	−0.4 (−1.3 to 0.5)	.03
Stage 2[a]	44	45	−0.8 (−1.6 to −0.1)	0.4 (−0.6 to 1.3)	.04	−1.2 (−2.4 to −0.1)	
10 wk[f]	93	66	−1.3 (−2.1 to −0.5)	0.1 (−0.7 to 0.8)	.03	−1.0 (−1.9 to −0.1)	NA
NPI Irritability/Lability domain[e]							
Stage 1[a]	93	125	−2.2 (−3.0 to −1.4)	−1.2 (−1.8 to −0.6)	.09	−0.7 (−1.5 to 0.1)	.03
Stage 2[a]	44	45	−1.0 (−2.0 to 0.04)	−0.7 (−1.8 to 0.5)	.14	−0.9 (−2.2 to 0.3)	
10 wk[f]	93	66	−2.4 (−3.3 to −1.6)	−1.8 (−2.8 to −0.7)	.38	−0.4 (−1.4 to 0.6)	NA
NPI4A composite[e]							
Stage 1[a]	93	125	−7.3 (−9.1 to −5.4)	−4.5 (−6.0 to −3.0)	.03	−2.4 (−4.6 to −0.2)	.001
Stage 2[a]	44	45	−4.8 (−6.9 to −2.7)	−1.4 (−3.8 to 1.0)	.01	−3.9 (−7.0 to −0.9)	
10 wk[f]	93	66	−8.5 (−10.4 to −6.7)	−5.0 (−7.4 to −2.5)	.01	−3.4 (−6.1 to −0.7)	NA
NPI4D composite[e]							
Stage 1[a]	93	125	−7.6 (−9.4 to −5.7)	−4.0 (−5.5 to −2.6)	.006	−3.0 (−5.1 to −0.9)	<.001
Stage 2[a]	44	45	−4.6 (−6.8 to −2.4)	−1.9 (−4.2 to 0.4)	.02	−3.5 (−6.5 to −0.5)	
10 wk[f]	93	66	−8.3 (−10.1 to −6.5)	−5.0 (−7.4 to −2.6)	.02	−3.0 (−5.5 to −0.4)	NA
NPI Caregiver Distress agitation score[e]							
Stage 1[a]	93	125	−1.4 (−1.6 to −1.0)	−0.6 (−0.8 to −0.4)	<.001	−0.7 (−1.0 to −0.3)	.01
Stage 2[a]	44	45	−0.5 (−0.9 to −0.004)	−0.7 (−1.2 to −0.2)	.49	−0.2 (−0.8 to 0.4)	
10 wk[f]	93	66	NA	NA	NA	NA	NA
NPI Caregiver Distress total score[e]							
Stage 1[a]	93	125	−6.6 (−8.2 to −5.0)	−3.6 (−4.8 to −2.5)	NA	NA	.01
Stage 2[a]	44	45	−2.6 (−4.3 to −1.0)	−2.0 (−3.8 to −0.3)	NA	NA	
10 wk[f]	93	66	NA	NA	NA	NA	NA
Caregiver Strain Index[e]							
Stage 1[a]	93	125	−1.2 (−1.7 to −0.7)	−0.6 (−0.9 to −0.2)	.03	−0.6 (−1.2 to −0.1)	.05
Stage 2[a]	44	45	−0.2 (−0.7 to 0.3)	0.1 (−0.5 to 0.6)	.42	−0.3 (−1.0 to 0.4)	
10 wk[f]	93	66	−1.2 (−1.7 to 0.6)	−0.4 (−0.9 to 1.3)	.04	−0.8 (−1.6 to −0.02)	NA
Cornell Scale for Depression in Dementia[g]							
Stage 1[a]	88	123	−1.0 (−1.8 to −0.3)	0.6 (−0.1 to 1.3)	.002	−1.6 (−2.5 to −0.6)	.02
Stage 2[a]	43	44	−0.9 (−1.8 to −0.004)	−0.7 (−1.5 to 0.1)	.75	−0.2 (−1.3 to 0.9)	
10 wk[f]	88	64	−1.2 (−2.0 to −0.4)	0.4 (−0.6 to 1.5)	.03	−1.3 (−2.6 to −0.1)	NA
ADCS Clinical Global Impression of Change score for agitation[h]							
Stage 1[a]	88	123	3.0 (2.8 to 3.3)	3.6 (3.4 to 3.8)	<.001	−0.6 (−0.9 to −0.3)	<.001
Stage 2[a]	42	42	3.3 (2.9 to 3.6)	3.7 (3.3 to 4.2)	.07	−0.5 (−1.0 to 0.1)	
10 wk[f]	82	59	2.7 (2.3 to 3.1)	3.3 (3.0 to 3.7)	.02	−0.5 (−0.9 to −0.1)	NA

(continued)

Table 2. Summary of Efficacy Outcome Measures in the Modified Intention-to-Treat Population (continued)

Outcome Measure and Study Stage[a]	No. of Participants		Change From Baseline, Mean (95% CI)		*P* Value by Stage[b]	Least Squares Mean Treatment Difference (95% CI)[c]	*P* Value by SPCD[b,d]
	Dextromethorphan-Quinidine	Placebo	Dextromethorphan-Quinidine	Placebo			
Patient Global Impression of Change[i]							
Stage 1[a]	88	123	3.1 (2.8 to 3.3)	3.6 (3.4 to 3.8)	.001	−0.6 (−0.9 to −0.2)	.001
Stage 2[a]	43	44	3.2 (2.8 to 3.6)	3.8 (3.3 to 4.2)	.04	−0.6 (−1.1 to −0.1)	
10 wk[f]	81	59	2.9 (2.7 to 3.2)	3.5 (3.2 to 3.8)	.007	−0.6 (−1.0 to −0.2)	NA
Quality of Life–Alzheimer Disease scale							
Patient[h]							
Stage 1[a]	87	116	1.3 (−0.03 to 2.6)	0.0 (−1.0 to 0.9)	.14	1.1 (−0.4 to 2.6)	.16
Stage 2[a]	40	40	1.5 (−0.1 to 3.1)	0.7 (−0.7 to 2.0)	.50	0.7 (−1.4 to 2.7)	
10 wk[f]	87	61	0.7 (−0.7 to 2.1)	0.5 (−1.1 to 2.0)	.96	−0.1 (−2.0 to 1.9)	NA
Caregiver[h,j]							
Stage 1[a]	88	123	0.4 (−0.5 to 1.3)	0.3 (−0.5 to 1.1)	.63	0.3 (−0.9 to 1.5)	.47
Stage 2[a]	43	43	−0.3 (−1.5 to 0.9)	0.9 (−0.4 to 2.2)	.24	1.1 (−2.8 to 0.7)	
10 wk[f]	88	64	1.3 (0.2 to 2.4)	0.9 (−0.5 to 2.4)	.28	0.9 (−0.7 to 2.6)	NA
ADCS Activities of Daily Living Inventory[h]							
Stage 1[a]	88	123	−0.9 (−1.8 to −0.04)	−0.8 (−1.5 to −0.1)	.90	−0.1 (−1.2 to 1.1)	.16
Stage 2[a]	43	44	−2.0 (−3.4 to −0.5)	−0.6 (−1.7 to 0.4)	.12	−1.4 (−3.1 to 0.4)	
10 wk[f]	88	64	−0.8 (−1.8 to 0.2)	−1.8 (−2.9 to 0.7)	.17	1.0 (−0.5 to 2.5)	NA
Mini-Mental State Examination total score[g]							
Stage 1[a]	88	122	0.2 (−0.4 to 0.9)	−0.3 (−0.8 to 0.2)	.20	0.5 (−0.3 to 1.3)	.05
Stage 2[a]	42	44	0.3 (−0.5 to 1.2)	−0.5 (−1.3 to 0.2)	.15	0.8 (−0.3 to 2.0)	
10 wk[f]	88	63	0.1 (−0.5 to 0.8)	−0.6 (−1.5 to 0.3)	.21	0.7 (−0.4 to 1.8)	NA
Alzheimer Disease Assessment Scale–Cognitive Subscale[h]							
Stage 1[a]	87	121	−0.9 (−2.5 to 0.6)	0.3 (−5.7 to 1.3)	.11	−1.4 (−3.0 to 0.3)	.20
Stage 2[a]	42	43	0.3 (−1.4 to 1.9)	0.8 (−0.7 to 2.3)	.64	−0.5 (−2.8 to 1.7)	
10 wk[f]	81	58	−0.7 (−1.9 to 0.7)	1.2 (−0.2 to 2.4)	.07	−1.7 (−3.5 to 0.2)	NA

Abbreviations: ADCS, Alzheimer Disease Cooperative Study; NA, not assessed; NPI, Neuropsychiatric Inventory; NPI4A, the sum of Neuropsychiatric Inventory Agitation/Aggression, Irritability/Lability, Aberrant Motor Behavior, and Anxiety domain scores; NPI4D, the sum of Neuropsychiatric Inventory Agitation/Aggression, Irritability/Lability, Aberrant Motor Behavior, and Disinhibition domain scores.

[a] Stage 1 includes all patients and measures change from stage 1 baseline to week 5 for each outcome. Stage 2 includes only rerandomized placebo nonresponders from stage 1 and measures change from stage 2 baseline (week 5) to week 10 for all outcomes except the Patient Global Impression of Change, which measures change from original stage 1 baseline to week 10.

[b] *P* value by stage for dextromethorphan-quinidine vs placebo is based on analysis of covariance with treatment as fixed effect and baseline as covariate; *P* value for SPCD analysis is based on ordinary least squares.

[c] Treatment difference = dextromethorphan-quinidine − placebo.

[d] Sequential parallel comparison design (SPCD) analysis was protocol specified for the primary efficacy analysis and combines results from all patients in stage 1 and from placebo nonresponders rerandomized in stage 2 based on a 50/50 weighting of the NPI Agitation/Aggression domain for each stage of the study.

[e] Assessed at baseline and weeks 1, 3, 5, 6, 8, and 10.

[f] The 10-week analysis includes only patients who continued their original treatment for their entire study participation (ie, took only dextromethorphan-quinidine or only placebo, thereby simulating a parallel-group design) and measures change from stage 1 baseline to week 10.

[g] Assessed at screening and weeks 5 and 10.

[h] Assessed at baseline and weeks 5 and 10.

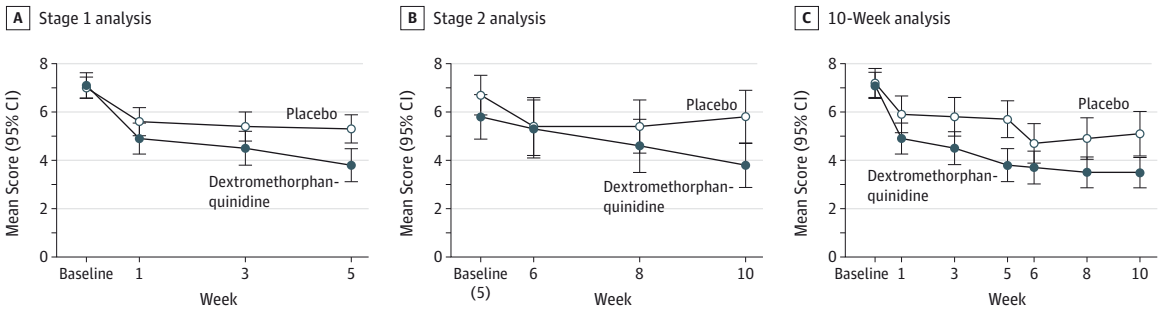
[i] Assessed at weeks 5 and 10.

[j] For the Quality of Life–Alzheimer Disease scale's caregiver response, the caregiver rates the patient's quality of life.

accident, aggression, and hematuria (n = 1 each). Serious adverse events in patients receiving placebo included idiopathic thrombocytopenic purpura, vertigo, pneumonia, gastroenteritis, contusion, transient ischemic attack, and agitation (n = 1 each). Eight patients (5.3%) receiving dextromethorphan-quinidine and 4 (3.1%) receiving placebo discontinued treatment owing to adverse events, including 4 (2.6%) and 2 (1.6%), respectively, for serious adverse events. No deaths occurred during the study.

Of the 13 patients who fell while receiving dextromethorphan-quinidine, 9 had a history of falls. Three fell 2 to 4 days after study completion, and 1 patient fell twice within 24 hours of

Figure 2. Mean Neuropsychiatric Inventory Agitation/Aggression Domain Scores by Stage and Visit for Patients Included in the Sequential Parallel Comparison Design and 10-Week Analyses



No. of participants[a]														
Dextromethorphan-quinidine	93	93	90	83	44	44	44	44	93	93	90	90	83	82	83
Placebo	125	124	121	119	45	45	45	45	66	65	65	65	60	60	60

A, Stage 1 (weeks 1-5); B, stage 2 (weeks 6-10) for placebo nonresponders rerandomized after stage 1; C, 10-week results (the 10-week secondary analysis includes only patients who continued the same treatment assignment throughout study participation; ie, were randomized to receive only dextromethorphan-quinidine or only placebo [excludes patients who were rerandomized from placebo to dextromethorphan-quinidine in stage 2], thus simulating a parallel-group design). Analysis-of-covariance models with treatment as fixed effect and baseline as covariate were used to compare mean change from baseline between groups at each time point. Baseline for stage 2 is the patients' scores at the start of stage 2. Least squares mean treatment differences are as follows: for stage 1, week 1, −0.8 (95% CI, −1.5 to −0.03; $P = .04$), week 3, −1.0 (95% CI, −1.8 to −0.2; $P = .01$), and week 5, −1.5 (95% CI, −2.3 to −0.7; $P < .001$); for stage 2, week 6, 0.7 (95% CI, −0.4 to 1.9; $P = .19$), week 8, −0.1 (95% CI, −1.3 to 1.2; $P = .93$), and week 10, −1.6 (95% CI, −2.9 to −0.3; $P = .02$); for 10-week analysis, week 1, −0.9 (95% CI, −1.8 to −0.04; $P = .047$), week 3, −1.3 (95% CI, −2.2 to −0.3; $P = .01$), week 5, −1.8 (95% CI, −2.7 to −0.9; $P < .001$), week 6, −0.9 (95% CI, −2.0 to 0.1; $P = .06$), week 8, −1.3 (95% CI, −2.4 to −0.3; $P = .01$), and week 10, −1.8 (95% CI, −2.8 to −0.7; $P = .003$).

[a] Observed cases.

receiving lorazepam rescue in both instances; no patient who fell while receiving placebo had a history of falls. Two falls were associated with serious adverse events; femur fracture in the dextromethorphan-quinidine group and contusion in the placebo group.

No clinically meaningful between-group differences in electrocardiographic findings were observed. The mean change in QTcF was 5.3 (SD, 14.06) milliseconds among patients receiving dextromethorphan-quinidine (n = 138) and −0.3 (SD, 12.96) milliseconds among patients receiving placebo (n = 60) at the final visit. Fifteen patients (10.3%) receiving dextromethorphan-quinidine (n=145) and 8 (6.7%) receiving placebo (n=120) had a QTcF increase of at least 30 milliseconds at any visit; 1 patient receiving placebo had a QTcF increase of greater than 60 milliseconds. No patient had a QTcF greater than 500 milliseconds.

Discussion

In this placebo-controlled randomized trial of dextromethorphan-quinidine for agitation in Alzheimer disease, we enrolled patients with moderate to severe symptoms who required pharmacological intervention. The Alzheimer disease–related agitation characteristics of patients in this study were generally consistent with the recently proposed definition of agitation from the International Psychogeriatric Association (IPA),[27] although patient emotional distress was not directly measured. As in the current study, the IPA definition requires the presence of behaviors causing excess disability that are not due to another medical, psychiatric, or substance-related disorder. Agitated behaviors may include excessive motor activity, verbal aggression, or physical aggression.[27] Baseline agitation severity and NPI Agitation/Aggression scores were also generally consistent with those of participants in the Citalopram for Agitation in Alzheimer Disease study.[9] Treatment with dextromethorphan-quinidine in this study demonstrated statistically significant efficacy on the primary end point and the majority of secondary end points across multiple measures rated by both clinicians and caregivers.

Improvement in the NPI Agitation/Aggression domain was statistically significant at week 1 and at every time point until study end, with exception of weeks 6 and 8 (during stage 2). The effects were considered to be clinically meaningful as reflected by improvement in ADCS Clinical Global Impression of Change and Patient Global Impression of Change scores, as well as on the measures of Caregiver Strain Index and NPI Caregiver Distress score. At the end of the 10-week treatment, 45.1% of participants treated only with dextromethorphan-quinidine (n = 82) were judged to have a "moderate" or "marked" improvement on ADCS Clinical Global Impression of Change vs 27.1% of participants who took only placebo (n = 59; $P = .008$). Similar results were also observed for Patient Global Impression of Change. Percentage improvement on the NPI Agitation/Aggression scores from baseline and proportion of patients achieving standard thresholds of response (eg, 30% or 50% response) were also used to gauge relevance of clinical response. The NPI manual (http://npitest.net/faqs.html), for instance, suggests that a 30% decrease in scores is generally clinically meaningful.

In this study, patients treated with only dextromethorphan-quinidine had a mean 50.7% reduction in the NPI Agitation/

Table 3. Summary of Categorical Efficacy Outcome in the Modified Intention-to-Treat Population

Study Stage	Categorical Response	No. (%) of Participants	
		Dextromethorphan-Quinidine	Placebo
Clinical Global Impressions-Severity Score for Agitation			
Baseline	Moderately ill	61 (65.6)	77 (61.6)
	Markedly ill	28 (30.1)	38 (30.4)
	Severely ill	4 (4.3)	9 (7.2)
	Among the most extremely ill	0	1 (0.8)
Alzheimer Disease Cooperative Study-Clinical Global Impression of Change Score for Agitation			
Stage 1[a]	Marked improvement	8 (9.1)	1 (0.8)
	Moderate improvement	22 (25.0)	13 (10.6)
	Minimal improvement	28 (31.8)	43 (35.0)
	No change	22 (25.0)	48 (39.0)
	Minimal worsening	7 (8.0)	12 (9.8)
	Moderate worsening	1 (1.1)	6 (4.9)
	Marked worsening	0	0
Stage 2[b]	Marked improvement	0	4 (9.5)
	Moderate improvement	11 (26.2)	2 (4.8)
	Minimal improvement	15 (35.7)	8 (19.0)
	No change	11 (26.2)	19 (45.2)
	Minimal worsening	4 (9.5)	6 (14.3)
	Moderate worsening	1 (2.4)	2 (4.8)
	Marked worsening	0	1 (2.4)
10 wk[c]	Marked improvement	9 (11.0)	6 (10.2)
	Moderate improvement	28 (34.1)	10 (16.9)
	Minimal improvement	27 (32.9)	18 (30.5)
	No change	14 (17.1)	15 (25.4)
	Minimal worsening	2 (2.4)	9 (15.3)
	Moderate worsening	1 (1.2)	0
	Marked worsening	1 (1.2)	1 (1.7)
Patient Global Impression of Change Score			
Stage 1[a]	Very much improved	10 (11.4)	2 (1.6)
	Much improved	24 (27.3)	23 (18.7)
	Minimally improved	20 (22.7)	30 (24.4)
	No change	20 (22.7)	40 (32.5)
	Minimally worse	13 (14.8)	23 (18.7)
	Much worse	1 (1.1)	4 (3.3)
	Very much worse	0	1 (0.8)
Stage 2[b]	Very much improved	3 (7.0)	3 (6.8)
	Much improved	10 (23.3)	4 (9.1)
	Minimally improved	14 (32.6)	11 (25.0)
	No change	10 (23.3)	13 (29.5)
	Minimally worse	4 (9.3)	9 (20.5)
	Much worse	2 (4.7)	4 (9.1)
	Very much worse	0	0
10 wk[c]	Very much improved	9 (11.1)	5 (8.5)
	Much improved	26 (32.1)	9 (15.3)
	Minimally improved	25 (30.9)	17 (28.8)
	No change	13 (16.0)	14 (23.7)
	Minimally worse	5 (6.2)	10 (16.9)
	Much worse	3 (3.7)	4 (6.8)
	Very much worse	0	0

[a] Stage 1 includes all patients and measures change from stage 1 baseline to week 5 for each outcome.

[b] Stage 2 includes only rerandomized placebo nonresponders from stage 1 and measures change from stage 2 baseline (week 5) to week 10 for all outcomes except the Patient Global Impression of Change, which measures change from original stage 1 baseline to week 10.

[c] The 10-week analysis includes only patients who continued their original assigned treatment for their entire study participation (ie, took only dextromethorphan-quinidine or only placebo, thereby simulating a parallel-group design) and measures change from stage 1 baseline to week 10.

Aggression scores from baseline to week 10 compared with 26.4% treated with only placebo (P = .001); this placebo response would not be deemed clinically meaningful. With respect to standard response thresholds, in the 10-week analysis, 55.9% of patients treated with only dextromethorphan-quinidine experienced at least a 50% reduction in the NPI

Agitation/Aggression score from baseline compared with 37.9% of patients receiving only placebo (P = .03). Furthermore, 65.6% of patients treated with only dextromethorphan-quinidine had at least a 30% reduction in NPI Agitation/Aggression scores from baseline compared with 47% of patients receiving only placebo (P = .02). Rates of response at the end of stage 1 (week 5) were comparable with those reported for the 10-week analysis in magnitude and significance compared with placebo. Combined, these between-group comparisons of response suggest that treatment with dextromethorphan-quinidine was consistently associated with a meaningful improvement in agitation, and with a magnitude that compares favorably with that found in prior studies included in a review published by Soto et al.[28] Significant improvements were also seen in the NPI4A and NPI4D composite scores comprising symptoms commonly observed in patients with Alzheimer disease–related agitation (Table 2).[29]

Dextromethorphan-quinidine was generally well tolerated in this elderly population receiving multiple concomitant medications and was not associated with cognitive impairment. Few patients discontinued because of adverse events, and most adverse events, including low rates of dizziness and diarrhea, were consistent with those observed in dextromethorphan-quinidine trials for pseudobulbar affect.[14,30,31] Falls were more common among patients receiving dextromethorphan-quinidine; an imbalance in prerandomization risk of falls and approximately 25% greater patient-days of exposure to dextromethorphan-quinidine may have contributed to the higher rates compared with placebo.

Dextromethorphan, the neurologically active component of the dextromethorphan-quinidine combination, has activity at receptors involved in modulating glutamate, serotonin, norepinephrine, and potentially other neurotransmitters, although the exact mechanism of action responsible for the reduction of dementia-associated agitation is not known. In earlier clinical studies, agitation in the context of dementia has been improved with drugs acting on serotonin (citalopram)[9] or glutamate (memantine) receptors,[32] lending support to the hypothesis that dextromethorphan exerts therapeutic effects on dementia-associated agitation through these and perhaps other central nervous system receptors.

To our knowledge, this is the first dementia-related trial to use a sequential parallel comparison design, an enrichment design chosen to address the potential of high placebo-associated improvement, as observed in previous trials evaluating neuropsychiatric symptoms in Alzheimer disease.[33,34] In studies using this design, the first stage randomizes more patients to placebo than to active treatment. In the second stage, placebo nonresponders from stage 1 are rerandomized and are included in the primary analysis. Pooled analysis of both stages maximizes the power to detect treatment differences and reduces the required sample size.[16] Consistent with prior studies using this design, while the placebo response in stage 2 (−0.8) among placebo nonresponders was smaller than in stage 1 (−1.7) and the response to active drug was also smaller in stage 2, the difference between active drug and placebo was still significant and had a standardized effect size of −0.34 (the standardized effect size in stage 1 was −0.505). Treatment effect was evident in both stages (even when placebo responders were included in the stage 2 comparison, a prespecified exploratory analysis). Improvement in NPI Agitation/Aggression was observed at week 1 (stage 1 and 10-week analyses) with the lower dextromethorphan-quinidine dose (20/10 mg) and appeared to increase over time. An analysis comparing patients who remained in their original randomized treatment group for the full 10-week study, which was prespecified to simulate a conventional 10-week parallel design, also showed a clinically and statistically significant effect on the primary end point and most secondary outcome measures favoring dextromethorphan-quinidine over placebo, consistent with sequential parallel comparison design analysis findings. Although stratification by disease stage measures such as cognitive function and severity of agitation did not appear to affect response to dextromethorphan-quinidine, the number of patients included in some strata used for these analyses were small, requiring confirmation of this observation in larger trials.

Strengths of the study include (1) use of the sequential parallel comparison design, with the intention of increasing study power by minimizing the effect of placebo response; (2) allowance of stable concomitant medications (including psychotropics), which closely reflects everyday clinical practice and adds to generalizability; (3) a high retention rate (88.2% across 10 weeks); (4) blinding of study sites to all aspects of the sequential parallel comparison design; (5) corroboration of efficacy observed for the primary efficacy end point by prespecified sensitivity analyses; and (6) consistent results among multiple significant secondary outcomes and the primary efficacy end point.

Limitations of this trial include a duration limited to 10 weeks and a dose-escalation schedule that limited evaluation of dose-response relationships. Aspects of the trial design, such as the exclusion of concomitant drugs related to quinidine, tricyclic antidepressants, monoamine oxidase inhibitors, or phenothiazines, as well as specific electrocardiographic/cardiac parameters that restricted patient enrollment, may limit the generalizability of study findings. Treatment at experienced trial sites by specialized clinicians under a clinical protocol prescribing frequent assessments may not reflect general practice. In addition, the patient sample consisted predominantly of outpatients; agitation in residents of nursing homes was underrepresented (5.5% of study participants). The treatment response may not be readily generalizable to patients in nursing homes and should be further explored.

Conclusions

In this 10-week phase 2 randomized clinical trial of patients with probable Alzheimer disease, the combination of dextromethorphan-quinidine demonstrated clinically relevant efficacy for agitation and was generally well tolerated. These preliminary findings require confirmation in additional clinical trials with longer treatment duration.

ARTICLE INFORMATION

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Obtained funding: Siffert.
Administrative, technical, or material support: Nguyen, Shin, Tariot, Siffert.
Study supervision: Cummings, Scharre, Shin, Tariot, Siffert.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Cummings has received in-kind research support from Avid Radiopharmaceuticals and Teva Pharmaceuticals. He has provided consultation to AbbVie, Acadia, ADAMAS, Alzheon, Anavex, AstraZeneca, Avanir, Biogen-Idec, Biotie, Boehringer-Ingelheim, Chase, Eisai, Forum, Genentech, Grifols, Intracellular Therapies, Lilly, Lundbeck, Merck, Neurotrope, Novartis, Nutricia, Otsuka, Pfizer, Prana, QR Pharma, Resverlogix, Roche, Sonexa, Suven, Takeda, and Toyoma companies. He has provided consultation to GE Healthcare and MedAvante and owns stock in ADAMAS, Prana, Sonexa, MedAvante, Neurotrax, and Neurokos. Dr Cummings owns the copyright of the Neuropsychiatric Inventory. Dr Lyketsos reports receiving grant support (research or continuing medical education) from National Institute of Mental Health (NIMH), National Institute on Aging (NIA), Associated Jewish Federation of Baltimore, Weinberg Foundation, Forest, GlaxoSmithKline, Eisai, Pfizer, AstraZeneca, Lilly, Ortho-McNeil, Bristol-Myers Squibb, Novartis, National Football League, Elan, and Functional Neuromodulation. He has received payment as consultant or advisor for AstraZeneca, GlaxoSmithKline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Eli Lilly, Pfizer, Genentech, Elan, NFL Players Association, NFL Benefits Office, Avanir, Zinfandel, Bristol-Myers Squibb, AbbVie, Janssen, Orion, Otsuka, Servier, and Astellas and honoraria or travel support from Pfizer, Forest, GlaxoSmithKline, and Health Monitor. Dr Peskind receives research grant support from the Department of Veterans Affairs, NIA, Eli Lilly, and Accera and has received payment as a consultant to Avanir, Eli Lilly, and Takeda. Dr Porsteinsson reports receiving grants to his institution from AstraZeneca, Avanir, Baxter, Biogen, Bristol-Myers Squibb, Eisai, Elan, EnVivo, Genentech/Roche, Janssen Alzheimer Initiative, Medivation, Merck, Pfizer, Toyama, Transition Therapeutics, the National Institutes of Health (NIH), NIMH, NIA, and Department of Defense and being a paid consultant for Elan, Janssen Alzheimer Initiative, Lundbeck, Pfizer, and TransTech Pharma. He holds a membership on data and safety monitoring boards for Quintiles, Functional Neuromodulation, and the New York State Psychiatric Institute and has participated on a speaker's bureau for Forest and developed educational presentations for CME Inc and PeerView Institute. Dr Mintzer receives grant support from Takeda, Avanir, Genentech, NIA/NIH, Alzheimer's Disease Neuroimaging Initiative, Elan, Eli Lilly, Grifols, Pfizer, and Roche and is majority owner of BioPharma Connex; BioPharma Connex was involved in facilitating nursing home recruitment for this study. He is also vice president of medical affairs for NeuroQuest. Dr Scharre has received consulting fees from Eli Lilly, Brain Test, Lundbeck, Avanir, and the Alois Alzheimer Foundation and has received grants to his institution for research from Lundbeck, Merck, Eli Lilly, Forum, Brain Test, AstraZeneca, Phylogeny, and Avanir. Dr De La Gandara has received support for clinical trials from Avanir Pharmaceuticals Inc, Elan, Transition Therapeutics, Janssen, Pfizer, Eli Lilly, Avid Pharmaceuticals, Novartis, Eisai, Chase, Gliacure Inc, Bristol-Myers Squibb, Grifols, Merck, GlaxoSmith Kline, Myriad, and Forest. Dr Tariot has received consulting fees from AbbVie, AC Immune, Boehringer-Ingelheim, Chase Pharmaceuticals, CME Inc, Medavante, Otsuka, and Sanofi-Aventis. He has received consulting fees and research support from AstraZeneca, Avanir, Bristol-Myers Squibb, Cognoptix, Janssen, Merck, Roche, and Takeda and research support only from Baxter Healthcare Corp, Functional Neuromodulation, GE, Genentech, Novartis, Pfizer, and Targacept. Dr Tariot has received other research support from the NIA and Arizona Department of Health Services and holds stock options in ADAMAS. Dr Davis has been a paid consultant for Avanir Pharmaceuticals Inc since 2011 and advised in the design, statistical analysis plan, and interpretation of these study data. Dr Davis also consults for Avanir across all other development programs including programs in depression, pain, migraine, and Parkinson disease. Dr Davis is president of CSD Biostatistics Inc, a statistical consulting company providing services to numerous pharmaceutical and other health care companies. Ms Nguyen, Mr Shin, and Dr Siffert are employees of Avanir and may hold stock or options. No other disclosures are reported.

Funding/Support: This study was funded by Avanir Pharmaceuticals Inc.

Role of the Funder/Sponsor: Avanir Pharmaceuticals had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The sponsor had no veto rights regarding the decision to submit the manuscript for publication.

Previous Presentation: The data from this study have been partially presented at the 139th Annual Meeting of the American Neurological Association; Baltimore, Maryland; October 13, 2014; and at the 2015 annual Alzheimer's Association International Conference; Washington, DC; July 22, 2015.

Additional Contributions: We acknowledge Maurizio Fava, MD, Massachusetts General Hospital (protocol design); Shereen McIntyre, MBA, Avanir (clinical data management and data analysis); Nadine Knowles, BA, Avanir (project management, protocol development, study startup training); Andrea E. Formella, PharmD, BCPP, Avanir (editorial assistance); Shelby L. Woods, Avanir (publication project management); Catherine Trinh Nguyen, BS, BA, Avanir; Jessie C. Nguyen, BS, Avanir (clinical research associate); Viola de Jong, RPH, CCRA, Avanir, Julia Degenhard, NP, Cognitive Research Corp, and Deborah Lees, BSN, Cognitive Research Corp (clinical monitoring of study sites and data monitoring); Gary G. Kay, PhD, Cognitive Research Corp (training of clinical raters); Ammie Z. Hill, MD, MMS Holdings Inc (medical monitor); Harry Haber, MPH, MMS Holdings Inc, and Linda LaMoreaux, MPH, MMS Holdings Inc (statistical analysis). Medical writing assistance was provided by John H. Simmons, MD, Peloton Advantage LLC, and was supported by Avanir. These persons received no compensation apart from usual salary for their contributions. We are grateful to all of the patients, caregivers, and families who volunteered for this study and to the investigators and their teams who made the study conduct possible.

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