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Effect of Second Generation Antipsychotics on Caregiver Burden in Alzheimer Disease

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Abstract

Context—Alzheimer disease (AD) imposes a severe burden upon patients and their caregivers. Severity of psychiatric symptoms and behavioral disturbances are important determinants of caregivers' experience of burden. These symptoms may be improved with atypical antipsychotic treatment.

Objective—In this study we use data from the CATIE-AD trial to evaluate the effect of atypical antipsychotics as compared to placebo on the experiences of caregivers of outpatients with Alzheimer disease.

Design—We compared the effect of atypical antipsychotic drugs (olanzapine, risperidone or quetiapine) considered together as a group, to placebo, on experiences of caregivers of AD outpatients. We also evaluated whether improvement in patients' psychiatric and behavioral symptoms mediated the relationship between drug treatment and caregiver burden.

Setting—CATIE-AD included outpatients in usual care settings, and assessed treatment effectiveness over a nine-month period.

Participants—Data from CATIE-AD participants who had at least one post-baseline outcome assessment, and from their caregivers, were examined in an intention-to-treat analysis (ITT) (N=361), and then in a phase 1 only analysis including only observations while on the initially randomized drug (N=153).

Measures—The Burden Interview, Beck Depression Inventory, and the NPI Caregiver Distress Scale were used to evaluate caregiver burden.

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Results—In both ITT and phase 1-only analyses, caregivers of patients treated with second generation antipsychotics (SGAs) scored significantly lower than those on placebo on both the Burden Interview ($p = 0.009$) and the NPI Caregiver Distress Scale's scores ($p = 0.0209$). These differences appeared to have been mediated by lower levels of agitation, hostility, and psychotic distortions.

Conclusion—In AD patients with symptoms of psychosis, agitation or aggressive behavior, medications can have a small but significant impact on caregiver burden.

Keywords

Caregivers Burden; Alzheimer Disease; Antipsychotic

Alzheimer disease (AD), is a costly and debilitating illness.[1]. By mid century, 81 millions cases of dementia are expected worldwide[2], and the cost of their care will approache 200 billion dollars per year in the USA alone. AD imposes a severe burden on patients and their relatives, particularly those directly responsible for their care.

Caregivers of AD patients are often subject to enormous stress[3–7] and are at high risk for depression[8–13], increased utilization of health services[14, 15] and psychotropic medications[16, 17]. Adverse effects of caregiving are especially pronounced among those who care for patients with dementia[18], and they appear to have a higher than expected mortality[19].

Psychiatric and behavioral symptoms are common in patients with AD[20–22] and severity of psychiatric symptoms and behavioral disturbances have been reported as the main determinants of caregivers experiences of burden[23–25].

The National Institute of Mental Health (NIMH) Clinical Antipsychotic Trials of Intervention Effectiveness –Alzheimer Disease (CATIE-AD) study, a large NIMH-funded, randomized controlled trial was designed to compare the effectiveness of antipsychotic medications and placebo in patients with AD and psychosis or agitated/aggressive behavior[26]. In contrast to the usual efficacy trial, CATIE-AD included outpatients in usual care settings, and assessed treatment effectiveness on several clinical outcome measures over a nine-month intervention period. A recent report using the CATIE-AD data found that clinical symptoms such as anger, aggression, and paranoid ideas improved with atypical antipsychotic treatment although no differences were found among the different antipsychotic drugs on most clinical outcome measures[27]. Aditional recent analyses of data from CATIE-AD showed that severity of such psychiatric symptoms and behavioral disturbances are among the strongest clinical correlates of caregivers' experience of burden[25]. We thus hypothesize that since treatment with atypical antipsychotics alleviates these symptoms for patients they may also reduce caregiver burden.

Methods

Study Design

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)-AD study was a large NIMH-funded, randomized controlled trial designed to compare the effectiveness of 3 antipsychotic medications and placebo over 9 months in outpatients with AD with psychotic symptoms and/or agitated/aggressive behavior at 42 U.S. sites. Participants were initially randomly assigned to receive olanzapine, quetiapine, risperidone or placebo under double-blind conditions in a 2:2:2:3 allocation ratio (phase 1). Those whose initial, assigned treatments were discontinued (end of phase 1) could be randomly and double-blindly assigned to receive treatment with one of the two SGAs that they were not initially assigned to or with citalopram (phase 2). Participants receiving placebo in phase 1 received citalopram or one of the 3 SGAs in a 3:1:1:1 ratio in phase 2. Participants whose phase 2 treatments were discontinued could then be randomly assigned to open label treatment with one of the active agents not yet received (phase 3). Patients could be shifted at any time to open treatment with physician's choice of medication and continue data collection. We present data on both patients in the entire intention- to-treat sample (i.e., those who received at least one follow-up assessment regardless of actual treatment received) (N=361) as well as those assessed during treatment with the initially randomized drug (phase 1 only, N = 153).

The trial was designed to encourage prescribing as close as possible to typical clinical practices. Study physicians adjusted dosages based on their clinical judgments and participants' responses to treatment[28].

The study was reviewed and approved by an Institutional Review Board (IRB) at each site. Written informed consent was obtained from the patients or their legally authorized representatives and from the partners or caregivers who participated with the patients. Details of the study design and entry criteria have been presented elsewhere[26, 28]. The current study relies on data collected at baseline, and 3, 6 and 9 months classified according to the original randomized group assignment, as well as limiting analysis to observations while patients were on their phase 1 drug.

Measures

Caregiver burden—The Burden Interview[29] is a widely used 22-item assessment tool for measuring caregivers' perceived burden from providing care in areas such as physical health, psychological well being, finances, and their interactions with the patient. Items are answered on a five-point scale ranging from 0= never to 4 = nearly always. Scores are added to give total score ranges from zero to 88, with higher scores implying greater perceived caregiver burden.

Caregiver Depression—The Beck Depression Inventory[30] includes 21 questions, with each response scored on a scale from 0 to 3. Higher total scores indicate more severe depressive symptoms.

Caregiver Distress—The Caregiver Distress Scale, is a composite of the scores based on the distress items of the Neuropsychiatric Inventory (NPI) described in greater detail below[31].

Psychiatric and behavioral symptoms in the patient were assessed with the Brief Psychiatric Rating Scale (BPRS;[32, 33]), in which a 7 point Likert scale is used to measure the severity of 18 psychiatric and behavioral symptoms and includes five-factor subscales: Agitation; Hostile Suspiciousness; Psychosis; Withdrawn Depression; and Cognitive Dysfunction. Symptoms were also measured with the NPI[31], a measure of the frequency and severity of 12 psychiatric symptoms over the previous month. The items assess delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep disturbance, and appetite and eating disorder. Caregivers rate each symptom, in terms of both frequency (1 to 4) and severity (1 to 3) indicating their distress from each symptom on a scale from 0 (not distressing at all) to 5 (extremely distressing). The NPI symptom score is calculated by multiplying the scores for severity and frequency (range=0 if absent and 1–12 if present).

The Cornell Scale for Depression in Dementia (CSDD)[34] was used to measure patient mood symptoms, ideational disturbances of depression, and neurovegetative signs.

Cognitive functioning—Cognitive functioning was assessed with: 1) The Mini Mental State Examination (MMSE)[35], a brief 30-item measure of global cognitive ability and 2) the AD Assessment Scale –Cognitive Subscale (ADAS-Cog), an 11-item assessment of memory, language, visuoconstructive skill, and ideational praxis[36].

Activities of daily living—The AD Cooperative Study –Activities of Daily Living Scale (ADCS-ADL)[37] is an inventory of basic and instrumental functional skills and abilities.

Quality of life—The Alzheimer Disease Related Quality of Life (ADRQL)[38] measures health-related quality of life in patients with AD. Items assess behaviors that reflect social interaction, maintenance of interests, participation in activities, cheerfulness, and freedom from distress.

Level of needed care—The Dependence Scale[39] is a measure of the amount of caregiver assistance needed by the patient to accomplish daily activities. Based on an interview with the caregiver, the patient's Equivalent Institutional Care (EIC) level is derived as follows: Level 1= Limited home care (needs some help with activities such as shopping or housekeeping); Level 2= Supervised adult home care (supervised setting with constant companionship and regular help with cooking and housekeeping); Level 3= Health-related facility (24-hour supervision for personal care and safety). The Caregiver Activity Scale[40], represents the total time that the caregiver spends providing assistance for a patient over the past 24 hours in five care-need domains.

Data Analyses

First we compared baseline data between ITT groups who had at least one follow-up assessment (N = 361), and those with none (N= 60). using an analysis of variance

(ANOVA). Then to evaluate the randomization within this ITT sub sample, we used ANOVA to compare patients who were randomized to placebo (N = 124) to those randomized to a SGA (N = 237) on the same baseline variables.

Next we compared baseline data on patients in the Phase I only sample, i.e. patients who had at least one follow-up visit while on the randomly assigned treatment (N = 153) with study participants, who did not have follow-up data while on randomly assigned drug. (N = 268). In addition, to evaluate the randomization within the Phase I only sub-sample, we compared baseline characteristics of patients in this sub sample who were assign placebo (N = 45) to those assigned a SGA (N = 108).

The primary analysis compared the average differences in the three burden measures across all time points between patients who received antipsychotic or placebo treatment. All available follow-up data were used in both the intention to treat and the Phase 1-only analyses. We used longitudinal mixed models which adjusted for the correlatedness of observations from the same individuals with unique patient identifier modeled as a random intercept, and controlled for time and for the baseline value of each dependant variable. Because of small sample sizes of burden data on individual drugs we did not attempt to compare the effects of individual drugs against placebo.

For burden measures on which there was a significant treatment effect, we conducted further analyses to determine whether improvement in psychiatric and behavioral symptoms among the patients mediated the relationship between drug treatment and caregiver burden. In these analyses, we repeated the mixed model analyses described above but added the NPI and BPRS patient scores as time-varying covariates since they appeared to have improved with antipsychotic treatment in previously published analyses of CATIE AD data[27]. If the variable representing treatment was no longer significant after the inclusion of these covariates, we inferred that the added covariates mediated the relationship between medication treatment and burden. We then examined two further the models covarying for the BPRS and the NPI scores separately to test if either of these measures was an independent mediator of the relationship between medication and burden. If treatment became non significant in the model in which BPRS was entered alone, we further repeated the model to include each of the BPRS subsocres separately.

Results

Patient characteristics and treatment

Mean age of participants was 77.9 (SD 7.5) years; 56% were female; 21% were non-white. Overall, 77–85% of patients in each treatment group discontinued the Phase 1 medication treatment prior to the end of the 36-week study period. As reported in prior previously[28], the median duration of Phase 1 treatment was 7.1 weeks and did not differ significantly across treatment groups (median duration ranged from 5.3 to 8.1 weeks in the four groups). Data on patient participation and outcomes werewere reported previously[27, 28, 41].

Subgroup Characteristics at baseline

Comparisons of baseline data on patients in the ITT sample for whom we have follow up data with the rest of the sample showed that caregivers of patients who had follow-up data were significantly older and more likely to be spouses than children of their caregivers ($p = 0.05$) (Table 1). Patients included in the analyses also had significantly less severe general psychiatric symptoms and a higher quality of life at baseline. In the ITT sample baseline caregiver burden and distress scores were higher for patients assigned to placebo compared to those assigned to SGA although these differences were small in magnitude (data available from first author).

Comparisons of patients in the phase 1-only sample for whom we have follow-up data with those for whom no follow up data were available showed that significantly more patients who had follow-up assessments were married (65.7% vs. 47.7%); fewer were females (50.7% vs. 64.7%); more of their caregivers were spouses (61.7% vs. 35.1%) and fewer were children (25.7 vs. 45.9%). No significant differences in clinical variables were noted (Table 2). Among patients in the phase 1-only group, those who were randomized to placebo were significantly more likely to be black than those assigned to SGAs (13.0% vs. 28.9%) (Table 3.).

Burden outcome in the ITT and phase I only groups

Caregivers of patients in the ITT sample randomized to SGAs scored significantly lower on the Burden Interview (less burden) score ($p = 0.009$) and the NPI distress scale (less distress) ($p = 0.0209$) than those assigned to placebo. Effect sizes were small with 0.18 standard deviation unit differences for both measures. The differences in the caregiver depression mean scores, in contrast, were not significant (Table 4).

Burden outcome in the phase 1-only groups

The same pattern was observed in the phase 1-only sample. Caregivers of patients in the SGAs group scored significantly lower on both the burden interview score ($p = 0.0264$) and the NPI distress scale ($p = 0.0467$). Effect sizes appeared larger than in the ITT analysis but were still rather modest at 0.26 standard deviation units for the Burden Measure and 0.25 on the NPI distress scale. As in the ITT analysis the differences in depression scores were not significant (Table 5 and Figure 1).

To examine the mediating effect of the BPRS and the NPI on the relationship of treatment to the burden interview score in the phase 1-only sample, we first entered both the BPRS and the NPI into the model including the burden interview score. In this model, treatment was no longer significant ($p = 0.096$). We then entered the NPI score alone and treatment was again no longer significant ($p = 0.114$). In the model in which only the BPRS was entered, treatment remained significant ($p = 0.041$). Thus, reductions in NPI scores appears to have mediated the relationship between treatment and the measure of burden.

When we entered both the BPRS and the NPI in the model with the NPI distress scale as outcome, treatment was no longer significant ($p = 0.137$). We then entered the NPI only and treatment was again non-significant ($p = 0.130$). We also entered the BPRS only and

treatment was again not significant (p = 0.112). We therefore entered each of the BPRS five subscales separately. In the models including BPRS agitation (p = 0.154), hostile suspiciousness (p = 0.218), and psychotic distortion (p = 0.152) subscores treatment was not significant while in the models including withdrawn depression (p = 0.017) and cognitive dysfunction (p = 0.047), treatment remained significant.

Discussion

In this study both the ITT analysis, and the Phase 1 –only analysis, caregivers of patients assigned to take antipsychotic medications had lower burden scores than those randomized to placebo. Effect sizes were statistically significant but small, at about 0.18 at the ITT analysis to 0.25 on the Phase-I only analysis.

These findings are encouraging since the original analyses from CATIE-AD found no overall benefit for antipsychotics as compared to placebo on either the primary study outcome, time to all cause medication discontinuation[28] or on a measure of Quality Adjusted Life Years used in the Cost Effectiveness analysis[42]. However, a recent publication on more specific clinical outcomes ratings in CATIE-AD[27] showed small benefits for medication over placebo on two measures of psychiatric symptoms, the BPRS, the NPI, as well as the clinician-rated Clinical Global Impression of Change during phase 1 of the trial. Taken together with the results of this study there appears to be some clinical benefit for both patients and caregivers favoring the medications, especially early in treatment.

The effect of SGAs on caregiver measures seems to have been mediated by improvement in psychiatric symptoms, more specifically agitation, hostile suspiciousness, and psychotic distortion. Hence, this study thus suggests that improvements in these symptoms may lead to reduced burden and distress for caregivers, although not to reduced depression.

Previous studies have also clearly shown that severity of psychiatric symptoms and behavioral disturbances are the main correlates of caregivers' experience of burden[23, 25] and we thus hypothesized that treatment with atypical antipsychotics might both alleviate these symptoms for patients and reduce caregivers burden. Our data showing significant, if small, reduction of burden indicators even in the presence of small degrees of clinical improvement and suggest a high sensitivity of caregiver burden to even small changes in patient clinical status.

The lack of medication effects on caregivers' depression is not surprising in light of earlier findings of weaker correlations between behavioral disturbances and caregivers depression[23, 25]. This also supports the notion that depression in caregivers might be distinct from burden and implies the need for different treatment. Despite the correlation of caregiver depression with psychiatric symptoms in AD patients, alleviation of these symptoms does not seem to have a direct effect on depression.

While antipsychotics have been shown to have a positive impact on behavioral symptoms in some clinical trials, their overall efficacy may be offset by adverse events that require medication discontinuation[28], a phenomenon that was clearly evident in the short treatment durations observed in the CATIE AD trial. Additionally, studies have shown that that

caregivers consider improvement in their relatives' quality of life, an outcome not affected by medication in the CATIE AD trial, to be as important as prolonging the patient's life, and that improvement in quality of life is more important to caregivers than either lengthening survival time or delaying admission to a nursing home[43]. A measure of Alzheimer disease related quality of life addressing issues such as social interaction, maintaining interests, and participating in activities was shown to be a robust predictor of reduced caregiver burden (Mohamed, Rosenheck et al. under review). Since antipsychotic medications were not beneficial in improving quality of life in phase 1 of CATIE AD[27], psychosocial interventions designed to improve patients' quality of life, perhaps through increased socialization and social interactions, may prove more powerful in reducing caregiver burden[44–46].

Two notable methodological limitations require comment. Since some measures of patient symptoms were based on the caregiver reports, it is possible that caregiver ratings of the severity of these symptoms reflect, at least in part, their own emotional state. However, the use of proxy reporting is unavoidable in AD research and the use of multiple measures of both patients symptoms and caregivers distress reduces the impact of this limitation. A second limitation is the small sample size, especially in the placebo comparison group. However a clear and statistically significant signal of reduced burden in association with antipsychotic therapy was detected in this study.

We conclude that among AD patients with symptoms of psychosis, agitation or aggressive behavior, atypical antipsychotic medications may reduce agitation, suspiciousness, and psychosis enough to have a small but significant impact on caregivers' experience of burden.

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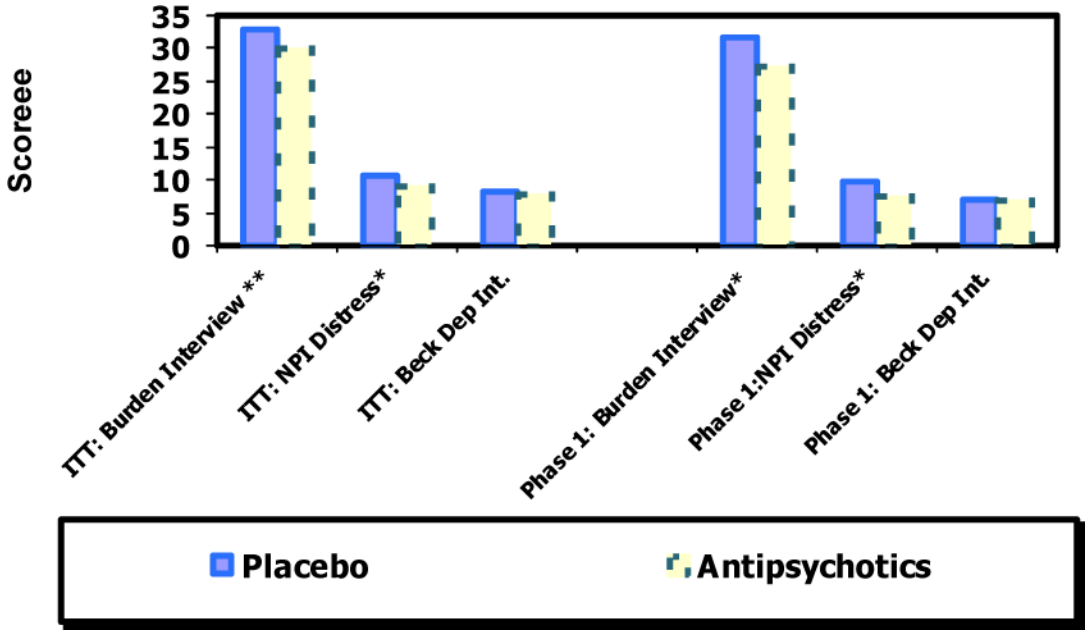

Figure 1.

Least square means comaprison of placebo and antipsychotics: Intention to treat (ITT) and Phase 1 only

Table 1

Comparison of baseline characteristics of the ITT sample with follow up data and the remainder of trial participants without follow up data.

	Included			Excluded		
	N	**%**	**Mean (SD)**	**N**	**%**	**Mean (SD)**
Patients Sociodemographic Characteristics	361	280 (77.6%)		60	51 (85.0%)	
White Race	361	280 (77.6%)		60	51 (85.0%)	
Age	361		77.8 (7.4)	60		78.2 (7.5)
Female	361	198 (54.8%)		60	37 (61.7%)	
Race/Ethnicity						
White Race	361	280 (77.6%)		60	51 (85.0%)	
Black Race	361	67 (18.6%)		60	8 (13.3%)	
Marital Status						
Married	361	219 (60.7%)		60		30 (50.0)
Education	348		12.3 (3.3)	57		11.8 (3.3)
Caregivers Sociodemographic Characteristics						
Age*	233		63.7 (15.0)	38		58.0 (17.6)
Female Sex	270	194 (71.9%)		49	32 (65.3%)	
Relationship with Patient						
Spouse*	317	150 (56.)%)		49	16 (32.7%)	
Child*	268	80 (29.9%)		49	24 (49.0%)	
Psychiatric and Behavioral Symptoms						
Neuropsychiatric Inventory (NPI)	358		36.3 (18.0)	56		40.4 (20.1)
Brief Psychiatric Rating Scale (BPRS)**	359		27.1 (12.1)	60		31.6 (13.0)
Cornell Scale for Depression in Dementia (CSDD)	357		9.8 (5.4)	59		10.4 (5.9)
Cognitive Skills						
Mini Mental State Examination (MMSE)	359		15.1 (5.6)	57		14.5 (6.9)
AD Assessment Scale –Cognitive Subscale (ADAS-Cog)	334		34.5 (13.1)	47		35.4 (14.6)
Functional Abilities						
AD Cooperative Study –Activities of Daily Living Scale (ADCS-ADL)	357		39.7 (16.8)	56		35.0 (19.4)
Quality of Life						
AD-Related Quality of Life*	358		68.0 (14.0)	58		63.3 (16.8)

	Included			Excluded		
	N	%	Mean (SD)	N	%	Mean (SD)
Care Needs						
Dependence Scale	357		3.3 (1.0)	55		3.4 (1.1)
Equivalent Institutional Care	357		1.91 (0.64)	55		1.89 (0.71)
Caregivers Activity Scale	355		16.1 (11.7)	54		17.9 (13.2)
Caregivers Burden						
Burden Interview	356		33.9 (15.9)	53		37.6 (16.7)
NPI Distress Score	358		16.27 (8.5)	56		17.8 (9.0)
Beck Depression Inventory	356		8.2 (7.2)	54		9.7 (8.1)

*P = 0.05;

**p = 0.001

Table 2

Baseline Characteristics of Patients With Versus Without Follow-Up Caregiver Burden Data While Receiving Phase 1 Drug Treatment

Variable	N	Follow-Up Caregiver Burden Data Obtained	N	No Follow-Up Caregiver Burden Data Obtained
Patient sociodemographic characteristics				
Age, Mean (SD), y	268	77.5 (7.3)	153	78.6 (7.6)
Female sex, n (%)**	268	136 (50.7)	153	99 (64.7)
Race/ethnicity, n (%)				
White	268	212 (79.1)	153	119 (77.8)
Black	268	48 (17.9)	153	27 (17.6)
Marital Status, married, n (%)***	268	176 (65.7)	153	73 (47.7)
Caregiver sociodemographic characteristics				
Age, Mean (SD), y	180	63.8 (15.4)	91	61.0 (15.7)
Female sex, n (%)	207	147 (71.0)	112	79 (70.5)
Education, mean (SD), y	260	12.4 (3.4)	145	11.9 (3.4)
Caregiver relationship with patient, n (%)				
Spouse***	206	127 (61.7)	111	39 (35.1)
Child***	206	53 (25.7)	111	51 (45.9)
Patient psychiatric and behavioral symptom scores, mean (SD)				
Neuropsychiatric Inventory	265	38.0 (17.6)	149	35.0 (19.0)
Brief Psychiatric Rating Scale	267	27.3 (11.5)	152	28.6 (13.6)
Cornell Scale for Depression in Dementia	265	10.2 (5.2)	151	9.5 (6.0)
Patient cognitive skills scores, mean (SD)				
Mini-Mental State Examination	267	15.2 (5.8)	149	14.7 (5.8)
Alzheimer's Disease Cooperative Study – Activities of Daily Living scale	252	34.8 (13.1)	129	13.7 (1.2)
Patient functional abilities score, mean (SD)				
Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale	266	39.3 (16.6)	147	38.6 (18.4)
Patient quality-of-life score, mean (SD)				
Alzheimer's Disease Related Quality of Life scale	266	67.0 (13.6)	150	67.9 (16.4)
Patient care-needs scores, mean (SD)				
Dependence Scale	265	3.3 (1.0)	147	3.3 (1.0)
Equivalent Institutional Care level*	265	2.0 (0.6)	147	7.8 (0.7)
Caregiver Activity Survey	263	16.5 (11.8)	146	16.0 (12.1)
Caregiver burden scores, mean (SD)				
Burden Interview	265	35.1 (15.6)	144	33.2 (16.6)
Neuropsychiatric Inventory Caregiver Distress Scale	265	16.9 (8.5)	149	15.7 (8.6)
Beck Depression Inventory	255	8.6 (7.2)	145	8.0 (7.5)

* P<.05, *t* test comparing the 2 groups

** P<.001, *t* test comparing the 2 groups

***P<.0001, *t* test comparing the 2 groups

Table 3

Baseline Characteristics of Patients Included in the Phase I Sample Randomized to Medication vs. vs those Randomized to Placebo

		Drugs		Placebo
Patients Sociodemographic Characteristics				
White Race				
Age	108	78.3 (7.9)	45	79.1 (7.0)
Female	108	69 (63.9%)	45	30 (66.7%)
Race/Ethnicity				
White Race	108	88 (81.5%)	45	31 (68.9%)
Black Race*	108	14 (13.0%)	45	13 (28.9%)
Marital Status				
Married	108	51 (47.2%)	45	22 (48.9%)
Education	101	12.0 (3.6)	44	11.7 (2.8)
Caregivers Sociodemographic Characteristics				
Age	62	59.4 (16.0)	29	64.5 (14.6)
Female Sex	79	54 (68.4%)	33	25 (75.8%)
Education	101	12.0 (3.4)	44	11.7 (2.8)
Relationship with Patient				
Spouse	78	27 (34.6%)	33	12 (36.4%)
Child	78	38 (48.7%)	33	13 (39.4%)
Psychiatric and Behavioral Symptoms				
Neuropsychiatric Inventory (NPI)	104	35.8 (19.2)	45	33.1 (19.6)
Brief Psychiatric Rating Scale (BPRS)	107	28.4 (13.4)	45	28.9 (14.2)
Cornell Scale for Depression in Dementia (CSDD)	106	9.5 (5.9)	45	9.4 (6.2)
Cognitive Skills				
Mini Mental State Examination (MMSE)	106	14.9 (5.9)	43	14.3 (5.8)
AD Assessment Scale – Cognitive Subscale (ADAS-Cog)	90	33.7 (14.2)	39	35.2 (12.6)
Functional Abilities				
AD Cooperative Study – Activities of Daily Living Scale (ADCS-ADL)	105	39.0 (19.3)	42	37.7 (16.2)
Quality of Life				
AD-Related Quality of Life	108	68.3 (16.5)	42	66.8 (16.2)
Care Needs				
Dependence Scale	105	3.3 (1.0)	42	3.2 (0.8)
Equivalent Institutional Care	105	1.8 (0.7)	42	1.8 (0.6)
Caregivers Activity Scale	104	15.7 (12.4)	42	16.6 (11.2)
Hospitalization for at least 2 weeks				
Caregivers Burden				
Burden Interview	102	33.5 (16.4)	42	32.5 (17.5)
NPI Distress Score	104	16.1 (8.4)	45	14.7 (9.2)
Beck Depression Inventory	101	7.6 (7.4)	44	8.8 (7.9)

*P = 0.05

Table 4

Outcome of ITT Drugs vs. Placebo Groups

	Placebo LMS	Drugs LSM	t	P
Caregivers Burden				
Burden Interview	33.0	30.0	6.86	0.0090
NPI Distress Score	10.6	9.0	5.36	0.0209
Beck Depression Inventory	8.1	7.8	0.24	0.5185

LMS = Lease Square Mean values across all follow up data points adjusted for the basline value of the dependant vaiable.

Table 5

Outcome of Phase I Drugs vs. Placebo Groups

	Placebo LMS	Drugs LMS	t	P
Caregivers Burden				
Burden Interview	31.6	27.5	5.03	0.0264
NPI Distress Score	9.7	7.6	4.0	0.0467
Beck Depression Inventory	7.1	7.0	0.02	0.8826

LMS = Lease Square Mean values across all follow up data points adjusted for the basline value of the dependant vaiable.