Effect of Second-Generation Antipsychotics on Caregiver Burden in Alzheimer's Disease

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ABSTRACT

Background: Alzheimer's disease (AD) imposes a severe burden upon patients and their caregivers. Severity of psychiatric symptoms and behavioral disturbances is an important determinant of caregivers' experience of burden. These symptoms may be improved with atypical antipsychotic treatment.

Objective: Data from the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) trial were used to evaluate the effect of atypical antipsychotics versus placebo on the experiences of caregivers of outpatients with AD.

Method: We compared the effect of atypical antipsychotic drugs (olanzapine, risperidone, or quetiapine—considered together as a group) versus placebo on the experiences of caregivers of AD outpatients (diagnosed according to *DSM-IV-TR*). We also evaluated whether improvement in patients' psychiatric and behavioral symptoms mediated the relationship between drug treatment and caregiver burden. The CATIE-AD trial, conducted from April 2001 through November 2004, included outpatients (mean age = 77.9 years [SD = 7.5 years]) in usual care settings and assessed treatment effectiveness over a 9-month period at 42 US sites. In a set of secondary analyses, data from CATIE-AD participants who had at least 1 postbaseline outcome assessment and data from their caregivers were examined in an intention-to-treat (ITT) analysis (N = 361). A phase 1–only analysis was conducted including only observations while patients were receiving the initially randomized drug (N = 153). The Burden Interview, the Beck Depression Inventory, and the Neuropsychiatric Inventory (NPI) Caregiver Distress Scale were used to evaluate caregiver burden.

Results: In both ITT and phase 1–only analyses, caregivers of patients treated with second-generation antipsychotics scored significantly lower than caregivers of patients receiving placebo on both the Burden Interview ($P = .0090$) and the NPI Caregiver Distress Scale ($P = .0209$). 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.

J Clin Psychiatry 2012;73(1):121–128

Submitted: *September 12, 2010; accepted February 18, 2011.*
Online ahead of print: *September 6, 2011 (doi:10.4088/JCP.10m06574).*
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Alzheimer's disease (AD) is a costly and debilitating illness.[1] By the middle of this century, 81 million cases of dementia are expected worldwide,[2] and the cost of care will approach $200 billion per year in the United States alone. Alzheimer's disease 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] and for 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] a situation in which caregivers 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's Disease (CATIE-AD) trial,[26] a large NIMH-funded randomized controlled trial, was designed to compare the effectiveness of antipsychotic medications versus placebo in patients with AD and psychosis or agitated/aggressive behavior. 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 9-month intervention period.[26] A recent report[27] 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. Additional recent analyses[25] of data from CATIE-AD showed that severity of such psychiatric symptoms and behavioral disturbances is one of the strongest clinical correlates of caregivers' experience of burden. We thus hypothesize that, since treatment with atypical antipsychotics alleviates these symptoms for patients, this treatment with antipsychotics may also reduce caregiver burden.

METHOD

Study Design

The CATIE-AD trial (clinicaltrials.gov Identifier: NCT00015548), conducted from April 2001 through November 2004, was designed to compare the effectiveness of 3 antipsychotic medications and placebo over a period of 9 months at 42 US sites in outpatients with AD (diagnosed according to *DSM-IV-TR*) with psychotic symptoms and/or agitated/aggressive behavior. 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-blindedly assigned to receive

treatment with 1 of the 2 second-generation antipsychotics (SGAs) that they were not initially assigned to or with citalopram (phase 2). Participants receiving placebo in phase 1 received citalopram or 1 of the 3 SGAs in a 3:1:1:1 ratio, respectively, 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 the physician's choice of medication and have continuation of data collection. We present data from a set of secondary analyses on both patients in the entire intention-to-treat (ITT) sample (ie, those who received at least 1 follow-up assessment regardless of actual treatment received) (N = 361) and those assessed during treatment with the initially randomized drug (phase 1 only) (N = 153).

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

The study was reviewed and approved by an institutional review board 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 at 3, 6, and 9 months, classified according to the original randomized group assignment, as well as on 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 5-point scale ranging from 0 = never to 4 = nearly always. Scores are added to give total score ranges from 0 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),[31] described in greater detail below.

Psychiatric and behavioral symptoms. The patients' psychiatric and behavioral symptoms 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 which includes 5 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.

Clinical Points

- Alzheimer's disease (AD) imposes a severe burden on patients and their relatives, particularly those individuals directly responsible for patient care.
- Psychiatric and behavioral symptoms are the main correlates of caregiver burden.
- Among AD patients with symptoms of psychosis, agitation, or aggressive behavior, atypical antipsychotic medications may reduce agitation, suspiciousness, and psychosis enough to have significant, if small, impact on caregivers' experience of burden.
- Psychosocial interventions designed to improve patients' quality of life, eg, through increased socialization and social interactions, are also important in reducing caregiver burden.

The NPI 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 the symptom is absent and 1–12 if the symptom is present). The Cornell Scale for Depression in Dementia[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,[35] a brief 30-item measure of global cognitive ability and (2) the cognitive subscale of the Alzheimer's Disease Assessment Scale,[36] an 11-item assessment of memory, language, visuoconstructive skill, and ideational praxis.

Activities of daily living. The Alzheimer's Disease Cooperative Study-Activities of Daily Living scale[37] is an inventory of basic and instrumental functional skills and abilities.

Quality of life. The Alzheimer's Disease Related Quality of Life[38] scale 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. On the basis of the Dependence Scale interview with an informant, the clinician rates the patient's level of "equivalent institutional care." The equivalent institutional care 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);

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Table 1. Baseline Characteristics of the Intention-to-Treat (ITT) Sample, Who Had Follow-Up Data, Versus the Remainder of the Trial Participants, Who Had No Follow-Up Data

Variable	N	Included (ITT sample with follow-up data)	N	Excluded (no follow-up data)
Patient sociodemographic characteristics				
Age, mean (SD), y	361	77.8 (7.4)	60	78.2 (7.5)
Female sex, n (%)	361	198 (54.8)	60	37 (61.7)
Race/ethnicity, n (%)				
White	361	280 (77.6)	60	51 (85.0)
Black	361	67 (18.6)	60	8 (13.3)
Marital status, married, n (%)	361	219 (60.7)	60	30 (50.0)
Education, mean (SD), y	348	12.3 (3.3)	57	11.8 (3.3)
Caregiver sociodemographic characteristics				
Age, mean (SD), y*	233	63.7 (15.0)	38	58.0 (17.6)
Female sex, n (%)	270	194 (71.9)	49	32 (65.3)
Caregiver relationship with patient, n (%)				
Spouse*	268	150 (56.0)	49	16 (32.7)
Child*	268	80 (29.9)	49	24 (49.0)
Patient psychiatric and behavioral symptom scores, mean (SD)				
Neuropsychiatric Inventory	358	36.3 (18.0)	56	40.4 (20.1)
Brief Psychiatric Rating Scale**	359	27.1 (12.1)	60	31.6 (13.0)
Cornell Scale for Depression in Dementia	357	9.8 (5.4)	59	10.4 (5.9)
Patient cognitive skills scores, mean (SD)				
Mini-Mental State Examination	359	15.1 (5.6)	57	14.5 (6.9)
Alzheimer's Disease Assessment Scale-cognitive subscale	334	34.5 (13.1)	47	35.4 (14.6)
Patient functional abilities score, mean (SD)				
Alzheimer's Disease Cooperative Study-Activities of Daily Living scale	357	39.7 (16.8)	56	35.0 (19.4)
Patient quality-of-life score, mean (SD)				
Alzheimer's Disease Related Quality of Life scale*	358	68.0 (14.0)	58	63.3 (16.8)
Patient care-needs scores, mean (SD)				
Dependence Scale	357	3.3 (1.0)	55	3.4 (1.1)
Equivalent Institutional Care level	357	1.9 (0.6)	55	1.9 (0.7)
Caregiver Activity Survey	355	16.1 (11.7)	54	17.9 (13.2)
Caregiver burden scores, mean (SD)				
Burden Interview	356	33.9 (15.9)	53	37.6 (16.7)
Neuropsychiatric Inventory Caregiver Distress Scale	358	16.3 (8.5)	56	17.8 (9.0)
Beck Depression Inventory	356	8.2 (7.2)	54	9.7 (8.1)

*$P < .05$, t test comparing the 2 groups.
**$P < .001$, t test comparing the 2 groups.

and level 3 = health-related facility (24-hour supervision for personal care and safety). The Caregiver Activity Survey[40] measures the total time that the caregiver spends providing assistance for a patient over the past 24 hours in 5 care-need domains.

Data Analyses

First, we compared baseline data between the ITT group, who had at least 1 follow-up assessment (N = 361), and the group that had no follow-up data (N = 60) using analysis of variance. Then, to evaluate the randomization within the ITT subsample, we used analysis of variance to compare patients who were randomized to placebo (n = 124) to those who were randomized to an SGA (n = 237) on the same baseline variables.

Next, we compared baseline data on patients in the phase 1–only sample, ie, patients who had at least 1 follow-up visit while receiving the randomly assigned phase 1 treatment (N = 153), with study participants who did not have follow-up data while receiving the randomly assigned phase 1 drug (N = 268). In addition, to evaluate the randomization within the phase 1–only subsample, we compared baseline characteristics of patients in this subsample who were assigned to placebo (n = 45) with the baseline characteristics of those who were assigned to an SGA (n = 108).

The primary analysis compared the mean differences in the 3 burden measures across all time points for caregivers of patients who received antipsychotic treatment versus placebo treatment. All available follow-up data were used in both the ITT and phase 1–only analyses. We used longitudinal mixed models that adjusted for the correlatedness of observations from the same individuals, with unique patient identifier modeled as a random intercept, and controlled for time and baseline value of each dependant variable. Because of small sample sizes for burden data on individual drugs, we did not attempt to compare the effects of individual drugs against placebo.

For burden measures for 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 these scores appeared to have improved with antipsychotic treatment in previously published analyses of

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 Assessment Scale-cognitive subscale	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	1.8 (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.

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 2 further models, covarying for the BPRS and the NPI scores separately to test whether either of these measures was an independent mediator of the relationship between medication and burden. If treatment became nonsignificant in the model in which BPRS was entered alone, we further repeated the model to include each of the BPRS subscores separately.

RESULTS

Patient Characteristics and Treatment

Mean age of participants was 77.9 years (SD = 7.5 years); 56% were female; 21% were nonwhite. 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 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 4 groups). Data on patient participation and outcomes were 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 versus 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 ($P < .05$) (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 SGAs, 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 female (50.7% vs 64.7%), more of their caregivers were spouses (61.7% vs 35.1%),

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Table 3. Baseline Characteristics of Patients Who Were Randomized to Drug Treatment Versus Placebo in the Phase 1 Sample

Variable	N	Drug Group	N	Placebo Group
Patient sociodemographic characteristics				
Age, mean (SD), y	108	78.3 (7.9)	45	79.1 (7.0)
Female sex, n (%)	108	69 (63.9)	45	30 (66.7)
Race/ethnicity, n (%)				
White	108	88 (81.5)	45	31 (68.9)
Black*	108	14 (13.0)	45	13 (28.9)
Marital status, married, n (%)	108	51 (47.2)	45	22 (48.9)
Education, mean (SD), y	101	12.0 (3.6)	44	11.7 (2.8)
Caregiver sociodemographic characteristics				
Age, mean (SD), y	62	59.4 (16.0)	29	64.5 (14.6)
Female sex, n (%)	79	54 (68.4)	33	25 (75.8)
Education, mean (SD), y	101	12.0 (3.4)	44	11.7 (2.8)
Caregiver relationship with patient, n (%)				
Spouse	78	27 (34.6)	33	12 (36.4)
Child	78	38 (48.7)	33	13 (39.4)
Patient psychiatric and behavioral symptom scores, mean (SD)				
Neuropsychiatric Inventory	104	35.8 (19.2)	45	33.1 (19.6)
Brief Psychiatric Rating Scale	107	28.4 (13.4)	45	28.9 (14.2)
Cornell Scale for Depression in Dementia	106	9.5 (5.9)	45	9.4 (6.2)
Patient cognitive skills scores, mean (SD)				
Mini-Mental State Examination	106	14.9 (5.9)	43	14.3 (5.8)
Alzheimer's Disease Assessment Scale-cognitive subscale	90	33.7 (14.2)	39	35.2 (12.6)
Patient functional abilities score, mean (SD)				
Alzheimer's Disease Cooperative Study-Activities of Daily Living scale	105	39.0 (19.3)	42	37.7 (16.2)
Patient quality-of-life score, mean (SD)				
Alzheimer's Disease Related Quality of Life scale	108	68.3 (16.5)	42	66.8 (16.2)
Patient care-needs scores, mean (SD)				
Dependence Scale	105	3.3 (1.0)	42	3.2 (0.8)
Equivalent Institutional Care level	105	1.8 (0.7)	42	1.8 (0.6)
Caregiver Activity Survey	104	15.7 (12.4)	42	16.6 (11.2)
Caregiver burden scores, mean (SD)				
Burden Interview	102	33.5 (16.4)	42	32.5 (17.5)
Neuropsychiatric Inventory Caregiver Distress Scale	104	16.1 (8.4)	45	14.7 (9.2)
Beck Depression Inventory	101	7.6 (7.4)	44	8.8 (7.9)

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

and fewer caregivers 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 (28.9% vs 13.0%) (Table 3).

Burden Outcome in the ITT and Phase 1–Only Groups

Caregivers of patients in the ITT sample randomized to SGAs scored significantly lower on the Burden Interview (less burden) ($P = .0090$) and the NPI Caregiver Distress Scale (less distress) ($P = .0209$) than caregivers of those assigned to placebo. Effect sizes were small, with 0.18 SD unit differences for both measures. The differences in the caregiver mean depression scores, in contrast, were not significant (Table 4).

Burden Outcome in the Phase 1–Only Group

The same pattern was observed in the phase 1–only sample. Caregivers of patients in the SGA group scored significantly lower on both the Burden Interview ($P = .0264$) and the NPI Caregiver Distress Scale ($P = .0467$). Effect sizes appeared larger than in the ITT analysis but were still rather modest at 0.26 SD units for the burden measure and 0.25 for the 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 NPI on the relationship of treatment to the Burden Interview score in the phase 1–only sample, we first entered both the BPRS and NPI into the model including the Burden Interview score. In this model, treatment was no longer significant ($P = .096$). We then entered the NPI score alone, and treatment was again no longer significant ($P = .114$). In the model into which only the BPRS was entered, treatment remained significant ($P = .041$). Thus, reduction in NPI scores appears to have mediated the relationship between treatment and the measure of burden.

When we entered both the BPRS and NPI into the model, with the NPI Caregiver Distress Scale as the outcome, treatment was no longer significant ($P = .137$). We then entered the NPI only, and treatment was again nonsignificant ($P = .130$). We also entered the BPRS only, and treatment was again not significant ($P = .112$). We therefore entered each of the 5 BPRS subscales separately. In the models that included BPRS agitation ($P = .154$), hostile suspiciousness ($P = .218$), and psychotic distortion ($P = .152$) subscores, treatment was not significant, while, in the models including withdrawn

Table 4. Outcomes Among Caregivers of Alzheimer's Disease Patients in the Intention-to-Treat Drug Group (n = 237) Versus Placebo Group (n = 124)

Measure of Caregiver Burden	Placebo Group, Least-Squares Mean Score[a]	Drug Group, Least Squares Mean Score[a]	*t*	*P*
Burden Interview	33.0	30.0	6.86	.0090
NPI Caregiver Distress Scale	10.6	9.0	5.36	.0209
Beck Depression Inventory	8.1	7.8	0.24	.5185

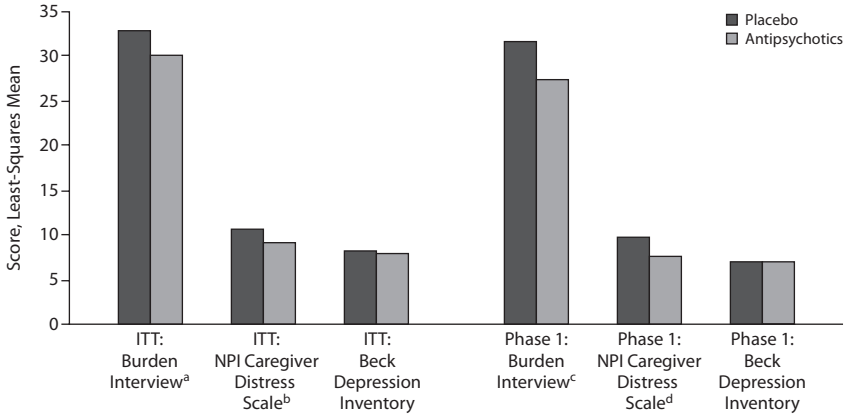
[a]Least-squares mean values across all follow-up datapoints, adjusted for the baseline value of the dependant variable.
Abbreviation: NPI = Neuropsychiatric Inventory.

Table 5. Outcomes Among Caregivers of Alzheimer's Disease Patients in the Phase 1 Drug Group (n = 108) Versus Placebo Group (n = 45)

Measure of Caregiver Burden	Placebo Group, Least-Squares Mean Score[a]	Drug Group, Least-Squares Mean Score[a]	*t*	*P*
Burden Interview	31.6	27.5	5.03	.0264
NPI Caregiver Distress Scale	9.7	7.6	4.00	.0467
Beck Depression Inventory	7.1	7.0	0.02	.8826

[a]Least-squares mean values across all follow-up datapoints, adjusted for the baseline value of the dependant variable.
Abbreviation: NPI = Neuropsychiatric Inventory.

Figure 1. Least-Squares Mean Comparison of Placebo and Antipsychotics for the Intention-to-Treat (N = 361) and Phase 1–Only (N = 153) Analyses



[a]*P* = .0090. [b]*P* = .0209. [c]*P* = .0264. [d]*P* = .0467.
Abbreviations: ITT = intention to treat, NPI = Neuropsychiatric Inventory.

depression (*P* = .017) and cognitive dysfunction (*P* = .047) subscores, treatment remained significant.

DISCUSSION

In this study, for both the ITT analysis and the phase 1–only analysis, caregivers of patients assigned to take antipsychotic medications had lower burden scores than caregivers of those randomized to placebo. Effect sizes were statistically significant but small, at about 0.18 for the ITT analysis to 0.25 for the phase 1–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 a measure of quality-adjusted life-years used in the cost-effectiveness analysis.[42] However, a recent publication[27] on more specific clinical outcome ratings in CATIE-AD showed small benefits for medication over placebo on 2 measures of psychiatric symptoms, the BPRS and the NPI, as well as on the clinician-rated Clinical Global Impression of Change[43] scale during phase 1 of the trial. When these findings are considered together with the results of this study, there appears to be some clinical benefit for both patients and caregivers in favor of 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 suggests that improvements in these symptoms may lead to reduced burden and distress for caregivers—although not to reduced depression.

Previous studies[23,25] have also clearly shown that severity of psychiatric symptoms and behavioral disturbances are the main correlates of caregivers' experience of burden, and we thus hypothesized that treatment with atypical antipsychotics might both alleviate these symptoms for patients and reduce caregivers' burden. Our data show 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 finding 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 in patients does not seem to have a direct effect on caregiver 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, it has been shown that caregivers consider improvement in their relative's 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.[44] A measure of AD-related quality of life that addresses issues such as social interaction, maintaining interests, and participating in activities was shown to be a robust predictor of reduced caregiver burden.[25] 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 to be more powerful in reducing caregiver burden.[45–47]

Notable methodological limitations require comment. All analyses were secondary analyses. Since some measures of patient symptoms were based on the caregivers' 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. Another 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.

Drug names: citalopram (Celexa and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

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Potential conflicts of interest: **Dr Rosenheck** has received research support from Eli Lilly, Janssen, AstraZeneca, and Wyeth (currently Pfizer); has been a consultant to GlaxoSmithKline, Bristol-Myers Squibb, Organon, and Janssen; and has provided expert testimony in matters pertaining to Eli Lilly, Eli Lilly Canada, Novapharm, Janssen-Ortho, and Janssen. **Dr Lyketsos** has received grant support (for research or CME) from the National Institute of Mental Health (NIMH), the National Institute on Aging, The Associated Jewish Federation of Baltimore, The Harry and Jeanette Weinberg Foundation, Forest, GlaxoSmithKline, Eisai, Pfizer, AstraZeneca, Eli Lilly, Ortho-McNeil, Bristol-Myers Squibb, Novartis, National Football League (NFL), and Elan; has received consulting fees from AstraZeneca, GlaxoSmithKline, Eisai, Elan, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth (currently Pfizer), Lundbeck, Merz, Eli Lilly, Genentech, Pfizer, NFL Players Association, and the NFL; and has received speaking honoraria or travel support from Pfizer, Forest, GlaxoSmithKline, and Health Monitor. **Dr Sultzer** has received research support from Eli Lilly and Forest Research Institute. **Dr Schneider** has received consulting fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Novartis, Johnson & Johnson, and Pfizer and has received research grant support from Novartis, Eli Lilly, and Pfizer. **Drs Mohamed** and **Kaczynski** have no potential conflicts of interest with regard to the subject of this article.

Funding/support: Conduct of the study was supported by grant N01 MH9001 from NIMH, the National Institutes of Health (NIH) (to Dr Schneider). Dr Schneider's efforts in writing the manuscript were partially supported by grant P50 AG05142 from NIH to the University of Southern California Alzheimer Disease Research Center, Los Angeles, California. Dr Mohamed's efforts in writing the manuscript were partially supported by a contract with Wyeth Pharmaceuticals (currently Pfizer), Madison, New Jersey. Dr Lyketsos' efforts in writing the manuscript were supported by grant P01 AG05146 from NIH to the Johns Hopkins University Alzheimer's Disease Research Center, Baltimore, Maryland. Dr Sultzer's efforts in writing the manuscript were partially supported by the Department of Veterans Affairs (Merit Review Program).
Disclaimer: None of the sponsors assisted in the preparation, review, or approval of the manuscript.

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