Placebo Effects in the Treatment of Noncognitive Symptoms of Alzheimer's Disease: Analysis of the CATIE-AD Data

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ABSTRACT

Objective: To compare symptom trajectories between placebo and active drug responders and to examine whether early placebo improvement would be associated with subsequent placebo response in the treatment of patients with behavioral and psychological symptoms of dementia.

Methods: A post hoc analysis of data from 371 patients with *DSM-IV* Alzheimer's disease in Phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness for Alzheimer's disease (CATIE-AD) (April 2001 to November 2004) was conducted. Patients were randomly assigned to double-blind treatment with olanzapine, quetiapine, risperidone, or placebo. Trajectories of change in Brief Psychiatric Rating Scale (BPRS) total scores were compared between placebo and active drug responders. The predictive power of improvement at week 2 for response at week 8 was investigated, and sensitivity and specificity of incremental 5% cutoff points between 5% and 25% reduction in BPRS total score at week 2 were calculated.

Results: There were no significant differences in symptom trajectories between placebo and active drug responders. BPRS score reduction at week 2 was significantly associated with placebo response at week 8 (odds ratio = 1.13; $P < .001$). Use of a cutoff of 10% showed the highest accuracy of 0.67 (sensitivity, 0.63; specificity, 0.70).

Conclusions: Symptom trajectories of improvement of behavioral and psychological symptoms of dementia follow the same pattern irrespective of treatment. A 10% improvement at week 2 was the most appropriate predictor of subsequent placebo response at week 8, which may indicate utility for the placebo lead-in phase to minimize future trial failures of treatment for noncognitive symptoms of Alzheimer's disease.

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As the number of aged people and those with dementia increases, psychopharmacologic treatment of behavioral and psychological symptoms of dementia (BPSD) becomes an ever more serious challenge. Response of these symptoms to psychotropic medications is often difficult to demonstrate, at least in part because of large placebo effects in this population,[1,2] which has resulted in a number of failed trials in which drugs have not shown superiority over placebo treatment.[3–5] Previous studies of placebo response in older people have largely been in depression, and there are few reports on the treatment of other symptoms in patients with dementia.[6] In light of a number of failed trials in the treatment of psychosis, agitation, and aggression in dementia,[7–11] one future strategy might be to screen out placebo responders at an early stage in order to optimize trial design.

Some recent clinical trials have included a lead-in phase, in which placebo is given to participants, in an effort to identify and exclude those who show the strongest placebo response. However, the criteria adopted for identification of such participants have generally been arbitrary (eg, those showing a more than 20% score reduction in the 21-item Hamilton Depression Rating Scale)[12,13] and have not been based on empirical data. Furthermore, use of such a lead-in phase has been reported in only a single dementia trial.[14] This issue is highly relevant in patients with Alzheimer's disease (AD), for whom placebo effects are large.[6] Systematic investigation of the magnitude and timing of the placebo response in patients with AD and how it differs from the response to active drug treatment would allow us to identify potential placebo responders more effectively and facilitate efforts to improve the precision of clinical trials in AD.

The Clinical Antipsychotic Trials in Intervention Effectiveness for Alzheimer's Disease (CATIE-AD) study has considerable potential utility in this respect, given its large sample size, serial assessments of target symptoms, and inclusion of a placebo arm.[15] We conducted a post hoc analysis of the CATIE-AD data to explore whether we could find robust evidence that could guide systematic screening of potential placebo responders in future trials with AD patients. First, we compared symptom trajectories in placebo and

Clinical Points

- Placebo response has not been well investigated among patients with behavioral and psychological symptoms of dementia (BPSD).
- We found that a 10% improvement at week 2 was the most appropriate predictor of subsequent placebo response at week 8.
- This cutoff may be a useful threshold for the placebo lead-in phase to minimize trial failures for BPSD treatment.

active drug responders. Second, we investigated what the optimal criteria for identification of eventual potential placebo responders would have been in these data. In this secondary analysis, missing values were handled by means of multiple imputation; in addition, available case analysis was conducted in light of a relatively high attrition rate in the CATIE-AD.

METHODS

Study Design

The CATIE-AD study (ClinicalTrials.gov identifier: NCT00015548) was funded by the National Institute of Mental Health to compare the effectiveness of different antipsychotic medications for individuals with AD; the study description has been detailed elsewhere.[15] The trial was conducted between April 2001 and November 2004 at 45 sites in the United States. The primary aim was to compare the efficacy and effectiveness of 3 atypical antipsychotics in outpatients with AD who had delusions, hallucinations, or agitation that was severe enough to warrant the use of antipsychotics. These problematic symptoms are sometimes collectively referred to as behavioral and psychological symptoms of dementia. In phase 1 of the study, patients were randomly assigned under a double-blind condition to receive olanzapine, quetiapine, risperidone, or placebo in a 2:2:2:3 ratio. No placebo lead-in phase was included in this study. Doses were adjusted on the basis of physicians' judgments and patients' responses, and, from 2 weeks onward, physicians could choose to move the patient to phase 2 if they judged initial treatment to be lacking in efficacy or tolerability. Patients who responded during phase 1 continued treatment for up to 36 weeks. Verbal and written informed consent was obtained from participants or their legally authorized representatives at study enrollment. The current analysis was restricted to phase 1 data, and no additional ethical approval was required, as all data were anonymized.

Participants

Inclusion criteria were a primary diagnosis of dementia of Alzheimer's type according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[16] or probable AD[17] on the basis of the history, physical examination, results of structural brain imaging, and a score on the Mini-Mental State Examination (MMSE)[18] of 5 to 26. The patients had delusions, hallucinations, aggression, or agitation severe enough to warrant medication treatment assessed on the basis of scores on the Brief Psychiatric Rating Scale (BPRS)[19] and the Neuropsychiatric Inventory (NPI).[20] Eligible patients had to be ambulatory and living at home or in residential care or an assisted living facility. Patients were excluded on the basis of a current or past history of schizophrenia, delirium, other types of dementia, or psychosis that could be accounted for by another medical condition. Patients were also excluded if they required psychiatric admission, were about to commence cholinesterase inhibitor or antidepressant medication, or had previously received 2 of the 3 atypical antipsychotics under study. Data used in this study were derived from the patients who received assessments with the BPRS or NPI at both baseline and week 2 in phase 1.

Treatment Intervention

Participants received 1 of the 3 atypical antipsychotics or placebo under the randomized and double-blind treatment condition. These medications were prepared in low-dose and high-dose identically appearing capsules that contained olanzapine (2.5 mg or 5 mg), quetiapine (25 mg or 50 mg), risperidone (0.5 mg or 1 mg), or placebo. The study physician selected the number of low- or high-dose capsules for initial treatment and could adjust the dose on the basis of their clinical judgment and patients' responses.

Assessment Measures

All outcome measures in the CATIE-AD study have been reported previously.[15] In this study, 2 clinical measures for BPSD were used: the BPRS and NPI. These measures were assessed at baseline and at up to week 36 of treatment. Response was defined as a 25% or more reduction in the BPRS or NPI total scores from baseline to week 8.

Statistical Analysis

First, scores on the BPRS and NPI at baseline and weeks 2, 4, 8, and 12 were extracted. Differences in the degree of change in BPRS and NPI scores over time in active drug and placebo groups were investigated using a mixed-effects model for repeated measures (MMRM) that contained treatment group (placebo or active drug) and treatment week and group-by-week interaction as factors. An unstructured covariance matrix was used. Degrees of freedom for the error term were adjusted with the Satterthwaite method. The same analysis was also conducted separately for each active drug (olanzapine, quetiapine, or risperidone) with available case analysis. Second, response rates were calculated for those taking placebo and active drugs and were compared using χ^2 tests. Third, multiple logistic regression analysis was performed to evaluate any association between placebo response and demographic and clinical characteristics that included baseline total BPRS or NPI scores, gender, age (years), race (ie, white or other), marital status (ie, married or not), baseline total MMSE score, Cornell Scale for

Table 1. Baseline Demographic and Clinical Characteristics of the Patients

	BPRS (N = 371)		NPI (N = 368)	
	Placebo Group (n = 126)	Active Drug Group (n = 245)	Placebo Group (n = 126)	Active Drug Group (n = 242)
Characteristic[a]				
Age, mean ± SD (range), y	77.3 ± 7.3 (56–94)[b]	77.9 ± 7.4 (51–103)[c]	77.1 ± 7.0 (56–92)[d]	77.9 ± 7.5 (51–103)[e]
Women, n (%)	72 (57.1)	136 (55.5)	72 (57.1)	135 (55.7)
Race, white, n (%)	92 (73.0)[f]	196 (80.0)	93 (73.8)[f]	193 (79.7)
Marital status, married, n (%)	74 (58.7)	148 (60.4)	73 (57.9)	147 (60.7)
BPRS or NPI total score, mean ± SD (range)	27.9 ± 11.4 (4–62)[b]	27.2 ± 12.0 (4–66)[c]	39 ± 17.9 (5–87)[d]	35.3 ± 17.8 (3–104)[e]
MMSE score, mean ± SD (range)	14.5 ± 5.3 (5–26)[b]	15.2 ± 5.7 (4–28)[c]	14.4 ± 5.3 (5–26)[d]	15.4 ± 5.6 (4–28)[e]
CSDD score, mean ± SD (range)	10.3 ± 5.3 (0–31)[b]	9.4 ± 5.1 (0–22)[c]	10.2 ± 4.9 (0–21)[d]	9.5 ± 5.1 (0–22)[e]
ADAS-Cog score, mean ± SD (range)	35.7 ± 12.3 (10–67)[g]	33.8 ± 13.2 (8–67)[h]	35.8 ± 12.3 (10–67)[d]	34.0 ± 13.4 (8–67)[e]

[a]There was 1 missing value for race and 3 missing values for the MMSE total score at baseline for both the BPRS and NPI analyses, respectively, and 7.2% (n = 27) and 7.6% (n = 28) missing values for the ADAS-Cog total score at baseline for the BPRS and NPI analyses, respectively. There were no missing values for remaining variables (age, sex).
[b]The data were available in 120 patients.
[c]The data were available in 233 patients.
[d]The data were available in 112 patients.
[e]The data were available in 214 patients.
[f]The data were available in 125 patients.
[g]The data were available in 116 patients.
[h]The data were available in 228 patients.
Abbreviations: ADAS-Cog = Alzheimer Disease Assessment Scale Cognitive subscale, BPRS = Brief Psychiatric Rating Scale, CSDD = Cornell Scale for Depression in Dementia, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, SD = standard deviation.

Depression in Dementia (CSDD),[21] the Alzheimer Disease Assessment Scale Cognitive subscale (ADAS-Cog),[18] and score change in the BPRS or NPI from baseline to week 2. Fourth, the prediction performance of binary classification in early placebo improvement at week 2, to predict response at week 8, was examined. To this end, sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) of the consecutive cutoff points in increments of 5% between a 5%–25% reduction in BPRS or NPI scores from baseline to week 2 were calculated. To seek the optimal cutoff point, both the accuracy, defined as (True Positive + True Negative)/Total N, and area under the curve (AUC) of receiver operating characteristic (ROC) were calculated.

Missing values were handled by means of multiple imputation, which involves filling in each missing value multiple times and setting multiple completed datasets. Estimates were then combined using the formulae developed by Rubin.[22] Multiple imputation was performed, using SAS, version 9.4 (SAS Institute Inc, Cary, North Carolina). To account for uncertainty in imputations, 100 imputed data sets were created using Proc MI (a procedure within SAS) with a Markov chain Monte Carlo (MCMC) imputation method. In the imputation step, 2 draws from posterior distributions (ie, 1 for regression parameters and the other for predicted value for missing data) are used to reflect the uncertainty. Multiple imputation also assumes that any missing mechanism is missing at random, in which missing data can be explained by observed data. In the case of this study, the imputation was single-chain done with 200 burn-in iterations, which are the default settings. The imputation was repeated 100 times, the resulting datasets were then analyzed, and the results pooled using Proc MIANALYZE. In addition, available case analysis was performed to see if the results would be altered by dropouts.

Other statistical analyses, including the additional available case analysis, were performed using SPSS version 22.0 (IBM, Armonk, New York). A P value of $< .05$ was considered statistically significant (2-tailed).

RESULTS

Subject Characteristics

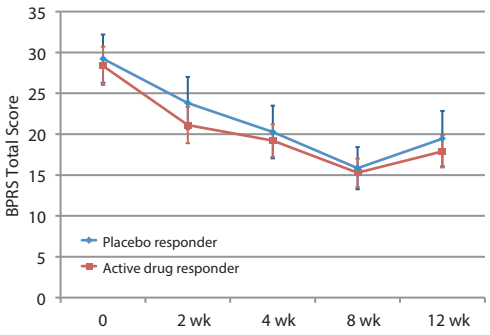
Three hundred seventy-one subjects (placebo, n = 126; active drug, n = 245) and 368 subjects (placebo, n = 126; active drug, n = 242) in the intention-to-treat (ITT) populations were included in the analyses for the BPRS and NPI, respectively. Demographic and clinical characteristics of the subjects are summarized in Table 1.

The missing proportions (out of a total of 371) for the BPRS imputation model were 28.3% at week 4, 51.5% at week 8, and 62.3% at week 12, while baseline BPRS values and week 2 values were available for all subjects. The corresponding figures (out of 368) for the NPI imputation model were 27.4%, 50.8%, and 62.2%, respectively, but baseline NPI values and week 2 values were complete. There were also a couple of missing values of minor significance, as indicated in Table 1.

Trajectories of Change in Psychiatric and Behavioral Symptoms in Responders

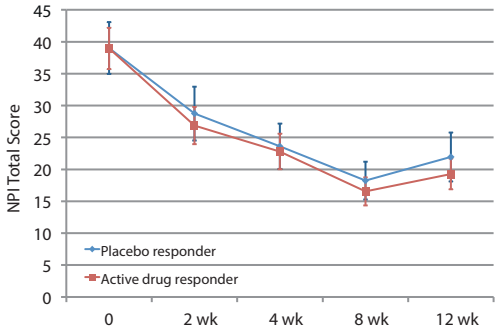
Figures 1 and 2 show trajectories of change in mean BPRS and NPI scores over time for placebo and active drug responders. There was no group-by-week interaction, indicating that the time courses of BPSD symptom improvement in AD were not significantly different between placebo and active drugs. Results with available case analysis were similar to these findings (Supplementary eFigures 1 and 2). There were also no significant group-by-week interactions when each active drug (olanzapine, quetiapine, or risperidone) was individually compared to placebo.

Figure 1. Trajectories of BPRS Total Scores in Placebo and Active Drug Responders (MI)[a]



[a]Vertical bars indicate standard deviations.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, MI = multiple imputation.

Figure 2. Trajectories of NPI Total Scores in Placebo and Active Drug Responders (MI)[a]



[a]Vertical bars indicate standard deviations.
Abbreviations: MI = multiple imputation, NPI = Neuropsychiatric Inventory.

Table 2. Association Between Demographic and Clinical Characteristics and Placebo Response[a,b] in BPRS and NPI at Week 8

	BPRS			NPI		
Variable	Odds Ratio	95% CI	*P* Value[c]	Odds Ratio	95% CI	*P* Value[c]
Age (per 1-year increment)	1.32	(0.58–2.99)	.510	1.67	(0.77–3.60)	.193
Sex						
Male	1 (reference)			1 (reference)		
Female	1.03	(0.63–1.69)	.902	0.78	(0.45–1.34)	.364
Race						
White	1 (reference)			1 (reference)		
Others	1.19	(0.68–2.11)	.544	1.32	(0.74–2.38)	.349
Marital status						
Married	1 (reference)			1 (reference)		
Not married	0.97	(0.59–1.57)	.895	0.85	(0.51–1.41)	.523
BPRS/NPI total score at baseline	1.02	(0.99–1.04)	.146	**1.02**	**(1.00–1.03)**	**.029**
BPRS/NPI total score reduction at week 2	**1.13**	**(1.08–1.18)**	**<.001**	**1.06**	**(1.04–1.09)**	**<.001**
MMSE total score at baseline	1.02	(0.97–1.07)	.439	1.04	(0.99–1.09)	.157
CSDD total score at baseline	1.00	(0.95–1.05)	.939	1.02	(0.97–1.07)	.519
ADAS-Cog total score at baseline	1.00	(0.98–1.02)	.700	0.98	(0.96–1.00)	.112

[a]Response was defined as a 25% or more reduction in the BPRS or NPI total score from baseline to week 8.
[b]Multiple imputation was used to deal with missing values.
[c]*P* value of <.05 is shown in bold.
Abbreviations: ADAS-Cog = Alzheimer Disease Assessment Scale Cognitive subscale, BPRS = Brief Psychiatric Rating Scale, CI = confidence interval, CSDD = Cornell Scale for Depression in Dementia, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory.

Response Rates

No statistically significant differences were found in the rates of responders in the BPRS or NPI between the placebo and active drug groups, although the rates were numerically higher in the active drug group (40.8% and 47.8% for BPRS; 55.2% and 58.0% for NPI, respectively).

Factors Associated With Response to Placebo at Week 8

The reductions in both BPRS and NPI total score at week 2 were significantly associated with subsequent response to placebo at week 8 (Table 2). NPI total score at baseline was also found to be significantly associated. Other examined factors failed to show any significant association with subsequent response at week 8. Available case analysis found similar findings with regard to the BPRS, whereas there was no significant association between any clinical factors and placebo response at week 8 in the NPI analysis (Supplementary eTable 1).

Power of Presence/Absence of Improvement at Week 2 to Predict Response at Week 8 With Placebo

The prediction performance of a binary outcome in the improvement at week 2 for placebo treatment at week 8 is shown in Table 3. The 10% and 5% cutoffs in the BPRS and the NPI, respectively, at week 2 showed the highest degree of accuracy for the prediction of placebo response at week 8. The ROC analysis demonstrated moderate values for the use of the BPRS and NPI total score reductions for the prediction of response at week 8, and these were 0.74 and 0.71, respectively. When available case analysis was employed, the 10% and 5% cutoffs in BPRS and NPI at week 2 showed the highest degree of accuracy for the prediction

Table 3. Prediction Performance of Score Reduction at Week 2 for Placebo Response[a,b] at Week 8

Rating Scale Used	Percentage Score Reduction at Week 2	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
BPRS (n = 126)	5%	0.71	0.63	0.62	0.72	0.667	
	10%	0.63	0.70	0.64	0.70	0.673	
	15%	0.57	0.75	0.66	0.68	0.667	0.74
	20%	0.49	0.80	0.67	0.65	0.656	
	25%	0.43	0.85	0.70	0.64	0.659	
NPI (n = 126)	5%	0.76	0.56	0.70	0.64	0.673	
	10%	0.70	0.61	0.70	0.61	0.665	
	15%	0.64	0.66	0.71	0.58	0.645	0.71
	20%	0.60	0.70	0.73	0.57	0.642	
	25%	0.53	0.74	0.73	0.54	0.620	

[a]Response was a 25% or more reduction in the BPRS or NPI total scores from baseline to week 8.
[b]Multiple imputation was used to deal with missing values.
Abbreviations: AUC = area under the curve, BPRS = Brief Psychiatric Rating Scale, NPI = Neuropsychiatric Inventory, NPV = negative predictive value, PPV = positive predictive value.

of placebo response at week 8, respectively (Supplementary eTable 2).

DISCUSSION

In the CATIE-AD study of patients with BPSD, placebo and active drug responders showed comparable trajectories in symptom improvement throughout the treatment period of 8 weeks and up to week 12. Initial improvement from baseline to week 2, as assessed by change in BPRS or NPI total score, predicted placebo response at week 8. Finally, a 10% reduction in the BPRS and 5% reduction in the NPI at week 2 were the best predictors of eventual placebo response at week 8.

Trajectories of Behavioral and Psychological Symptoms in AD

We found no significant differences in the trajectories of change of BPSD between placebo and active drug responders. This finding is consistent with what has been reported from studies of depression. Stassen et al[23] performed a meta-analysis of placebo-controlled double-blind randomized clinical trials comparing placebo and 2 antidepressants (oxaprotiline and amitriptyline) in major depressive disorder (MDD). They showed that the time course of recovery from depression followed the same pattern in the placebo and antidepressant treatment groups. The same authors reported on the analysis of 2,848 patients with MDD[24]; consistent with their earlier report, there were no significant differences in individual onsets of both improvement and response, defined as a ≥ 20% and a ≥ 50% baseline score reduction, respectively, between treatment modalities, while a significant difference was observed only in the proportions of responders (higher in the antidepressant group). They concluded that patients with depression were likely to possess a common, biological component that triggers recovery from depression regardless of drug type.[24]

Utility to Filter Out Potential Placebo Responders From Clinical Trials

As we had anticipated, reduction in BPRS and NPI total score at week 2 was found to be a significant predictor of subsequent placebo response at week 8. Total score reductions of 10% for BPRS and 5% for NPI at week 2 emerged as the best performing predictors of placebo response at week 8. Placebo response frequently makes the detection of additional "true" drug response difficult and is considered to be one of the reasons for an increasing number of negative trials.[3–5,7–11,25] Identifying factors that contribute to placebo effects has been a major focus of research interest, particularly in relation to the treatment of depression.[3,26,27] One approach that has been used to potentially minimize placebo response rates is to incorporate a single-blind, placebo lead-in phase (typically 7–14 days) into the study design, with the subsequent exclusion of placebo responders from randomization.[28,29] To our knowledge, only 1 trial for BPSD has included a placebo lead-in phase.[14] In this study to assess the efficacy and safety of olanzapine for these noncognitive symptoms of dementia, participants entered a 3- to 14-day, single-blind placebo lead-in period. Placebo response was defined as > 50% decrease in the summed score of the Neuropsychiatric Inventory-Nursing Home version (NPI/NH) items for core symptoms (agitation/aggression, hallucinations, and delusions). However, choice of the 50% cutoff was not supported by any empirical evidence and was completely arbitrary. Our findings, which suggest that cutoff points in the BPRS or NPI total score reduction at week 2 may be a more accurate predictor of placebo response at week 8, could serve as a benchmark for such trial designs. Further clinical trials are necessary to evaluate the usefulness of these cutoff values to more effectively exclude potential placebo responders.

Limitations

This study has several limitations. First, the CATIE-AD study was not originally designed to examine placebo response and symptom trajectories in patients with dementia. Second, the patients in this study were all limited to outpatients, and it will be important to further investigate this issue in other clinical populations, particularly patients with BPSD who have non-AD dementia and those resident in care facilities. Third, the choice of week 2 and week 8 time points for the current analysis was based on previous studies that examined

prediction performance in patients with schizophrenia and MDD[30,31] and is not necessarily optimal for AD patients. Fourth, there was a large amount of missing data for the BPRS and NPI scores at week 8. However, the findings using a multiple imputation method were similar to those obtained from available case analyses. Fifth, 3 antipsychotics were grouped into one for the purpose of analysis, although the original studies failed to find differential response across the drugs. Sixth, choice of variables included in the multiple logistic regression analysis was based on clinical relevance, but may be considered arbitrary. We included a limited number of variables in the analysis since inclusion of too many factors in one model could have resulted in low statistical power. Finally, it is important to point out that drug interventions should not be the first option for BPSD; they are reserved for those who have failed to respond to other nonpharmacologic approaches.[32]

CONCLUSION

The trajectories of change in psychological and behavioral symptoms in AD were similar between placebo responders and active drug responders. Cutoff scores of 10% total reduction in the BPRS and 5% in the NPI at week 2 were the most accurate predictors of subsequent response at week 8 in the treatment of BPSD. Although further prospective clinical trials are needed to confirm those preliminary findings, the results of this study provide critical insights in the design and conduct of future studies of noncognitive symptoms in patients with AD.

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Additional information: Data used in the preparation of this article were obtained from the limited access datasets distributed from the Clinical Antipsychotic Trials in Intervention Effectiveness with Alzheimer's Disease (CATIE-AD). This was a multisite, clinical trial of the treatment of noncognitive symptoms of Alzheimer's disease, comparing the effectiveness of randomly assigned medication treatment. The version of the dataset used was 1.0. Readers can find details on how to access the CATIE public access database at http://www.nimh.nih.gov/funding/clinical-research/datasets/nimh-procedures-for-requesting-data-sets.shtml.

Supplementary material: See accompanying pages.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

Supplementary material follows this article.

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Supplementary Material

Article Title: Placebo Effects in the Treatment of Noncognitive Symptoms of Alzheimer's Disease: Analysis of the CATIE-AD Data

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List of Supplementary Material for the article

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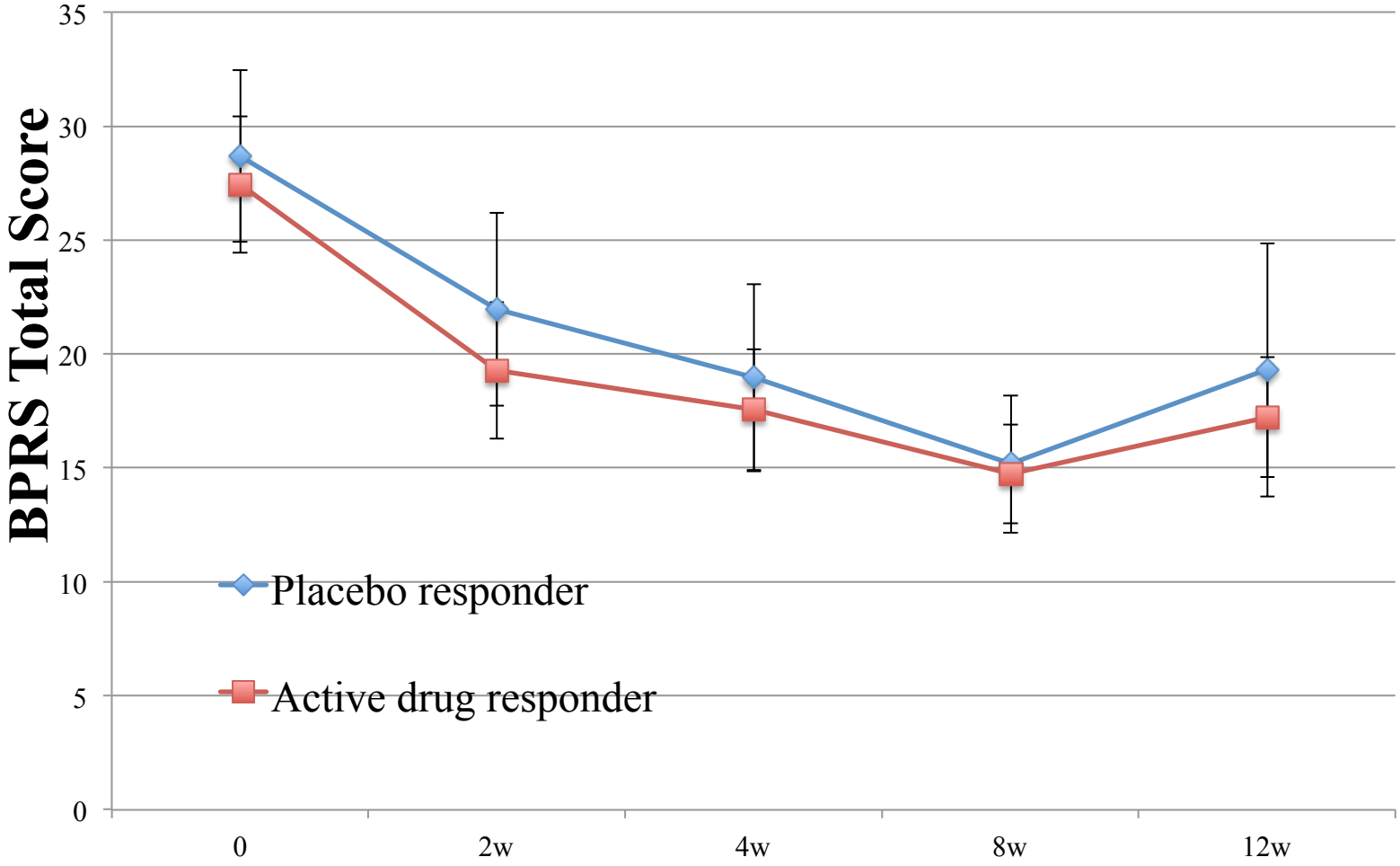
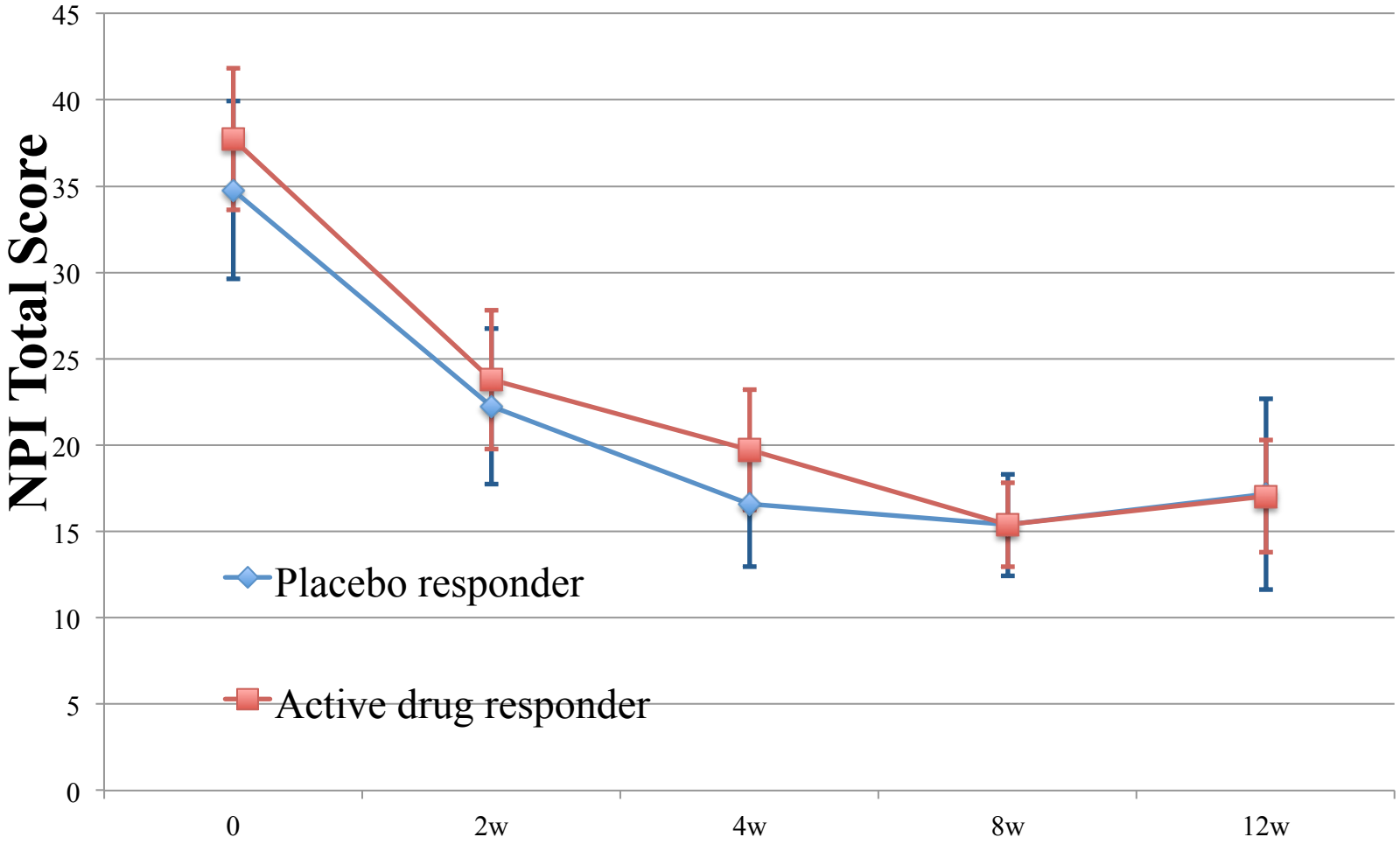
This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eFigure 1.
Trajectories of Mean Total Scores of BPRS(AC)



Abbreviations: AC, available case; BPRS, Brief Psychiatric Rating Scale
Vertical bars indicate standard deviations.

Supplementary eFigure 2.
Trajectories of Mean Total Scores of NPI (AC)



Abbreviations: AC, available case; NPI, Neuropsychiatric Inventory
Vertical bars indicate standard deviations.

Supplementary eTable 1. Association Between Demographic and Clinical Characteristics and Placebo Response[a] in BPRS and NPI at Week 8 (AC)

	Rating scale used					
	BPRS			NPI		
Variables	Odds Ratio	95%CI	p-value[b]	Odds Ratio	95%CI	p-value[b]
Age (years)	0.93	(0.84-1.04)	0.187	1.03	(0.95-1.13)	0.472
Sex						
Male	1 (reference)			1 (reference)		
Female	0.38	(0.085-1.66)	0.196	0.37	(0.09-1.46)	0.158
Race						
White	1 (reference)			1 (reference)		
Others	2.47	(0.57-10.8)	0.230	1.07	(0.29-4.04)	0.919
Marital status						
Married	1 (reference)			1 (reference)		
Not married	0.30	(0.065-1.43)	0.132	0.67	(0.18-2.49)	0.547
BPRS/NPI total score at baseline	1.03	(0.96-1.11)	0.426	1.02	(0.97-1.07)	0.546
BPRS/NPI total score reduction at week 2	**1.15**	**(1.03-1.28)**	**0.012**	1.04	(0.98-1.10)	0.163
MMSE total score at baseline	1.17	(0.96-1.44)	0.127	1.16	(0.95-1.41)	0.149
CSDD total score at baseline	0.87	(0.75-1.01)	0.072	0.96	(0.83-1.11)	0.580
ADAS-Cog total score at baseline	1.05	(0.96-1.14)	0.298	1.03	(0.96-1.11)	0.402

[a] Response was defined as a 25% or more reduction in the BPRS/NPI total score from baseline to week 8.

[b] p-value of <0.05 was shown in bold.

Abbreviations: AC, available case; ADAS-Cog, Alzheimer Disease Assessment Scale's Cognitive subscale; BPRS, Brief Psychiatric Rating Scale; CI, confidence interval; CSDD, Cornell Scale for Depression in Dementia; MMSE, Mini-Mental State Examination; NPI, the Neuropsychiatric Inventory

Supplementary eTable 2. Prediction Performance of Score Reduction at Week 2 for Placebo Response[a] at Week 8 (AC)

Rating scales used	Percentage score reduction at week 2	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
BPRS (n=126)	5%	0.71	0.56	0.57	0.70	0.629	
	10%	0.66	0.71	0.66	0.71	0.683	
	15%	0.59	0.74	0.65	0.68	0.667	0.81
	20%	0.45	0.79	0.65	0.63	0.634	
	25%	0.45	0.88	0.76	0.65	0.682	
NPI (n=126)	5%	0.80	0.33	0.67	0.50	0.625	
	10%	0.75	0.375	0.67	0.47	0.609	
	15%	0.72	0.42	0.67	0.48	0.603	0.60
	20%	0.60	0.46	0.65	0.41	0.547	
	25%	0.58	0.54	0.68	0.43	0.563	

[a] Response was a 25% or more reduction in the BPRS and NPI total scores from baseline to week 8

Abbreviations: AC, available case; AUC, area under the curve; BPRS, Brief Psychiatric Rating Scale; NPI, Neuropsychiatric Inventory; NPV, negative predictive value; PPV, positive predictive value