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Early Improvements of Individual Symptoms With Antipsychotics Predict Subsequent Treatment Response of Neuropsychiatric Symptoms in Alzheimer's Disease: A Re-Analysis of the CATIE-AD Study

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ABSTRACT

Objective: The aim of the present study was to identify individual symptoms whose early improvements contributed to subsequent treatment response to antipsychotics for neuropsychiatric symptoms (NPSs) in patients with Alzheimer's disease (AD) using the dataset of the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATIE-AD).

Methods: The CATIE-AD study was conducted between April 2001 and November 2004 at 45 sites in the United States. Data for 421 patients with *DSM-IV* AD with NPSs treated with antipsychotics were analyzed in the present study. Treatment response was defined as a reduction of ≥ 9 points in the Neuropsychiatric Inventory (NPI) score or a reduction of ≥ 25% from baseline in Brief Psychiatric Rating Scale (BPRS) total score at week 8. Logistic regression analyses were performed to examine associations between response and clinical and demographic characteristics, including each total or individual symptom score reduction at week 2.

Results: Reduction in NPI or BPRS total score at week 2 and several individual symptom score reductions (euphoria/elation, irritability, hallucinations, anxiety, agitation, apathy, disinhibition, and depression among NPI subitems; excitement, suspiciousness, disorientation, hostility, depressive mood, and emotional withdrawal among BPRS subitems) at week 2 were significantly associated with subsequent treatment response at week 8 (all *P* values < .05); Early non-improvements of irritability and suspiciousness were shown to be especially influential clinical markers in predicting subsequent treatment nonresponse. Furthermore, healthier condition at baseline was significantly associated with treatment response at week 8 (*P* < .05).

Conclusions: Although further research to validate these preliminary findings is needed, focusing on early improvements of individual symptoms could help identify subsequent treatment responders to antipsychotics in AD patients with NPSs.

Trial Registration: ClinicalTrials.gov identifier: NCT00015548

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Alzheimer's disease (AD) is a neurodegenerative disease characterized by neurocognitive impairment, which progressively impairs activities of daily living (ADL) including self-care, housework, and social activity.[1] During the long-term course of the disease, neuropsychiatric symptoms (NPSs), including psychosis, aggression, depression, disinhibition, and apathy, appear in patients with AD, which increases the distress of patients and their caregivers and accelerates institutionalization.[2] Although non-pharmacologic interventions are considered to be the first-line management of these NPSs, psychotropic medications are often necessitated in a real-world clinical setting.[3,4] Among them, antipsychotics are frequently used to manage NPSs; however, usage of antipsychotics for elderly patients is still controversial due to safety concerns such as increased mortality and adverse effects, particularly in patients with dementia.[5] Therefore, it is crucial to identify clinical predictors of response to antipsychotics to confirm the effectiveness (efficacy and tolerance) of antipsychotic treatment for NPSs in patients with AD.

Several studies[6–9] noted clinical predictors of subsequent favorable treatment outcomes of NPSs in patients with AD. A previous study[8] identified the following predictors at baseline for subsequent better treatment response at week 8: a lower global cognitive status, treatment with risperidone (versus olanzapine or quetiapine), past medical history of diabetes mellitus, healthier physical status, and severer initial psychotic symptoms of greater severity. Furthermore, recent studies demonstrated that early improvements of the symptoms by placebo may be clinical predictors of subsequent treatment response in patients with AD who had NPSs.[9] Moreover, such findings obtained from these AD studies are also found in other studies conducted in patients with schizophrenia.[10–12] All of the previous studies in AD, however, focused on early improvement of the overall severity of NPSs (eg, reduction in total scores on the Brief Psychiatric Scale [BPRS] or Neuropsychiatric

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Clinical Points

- To identify whether early improvements of individual symptoms could predict subsequent treatment response for neuropsychiatric symptoms in patients with Alzheimer's disease, this study analyzed the CATIE-AD phase 1 dataset.
- Predicting poor outcomes related to early non-improvements in several individual neuropsychiatric symptoms can protect patients from excessive exposure to antipsychotics that are unlikely to have a beneficial impact on patients.

Inventory [NPI] from baseline to endpoint) as a clinical predictor of subsequent treatment outcomes rather than individual NPSs in patients with AD.[9] Given limited time in the daily clinical practice, it is helpful for clinicians to be able to predict a more detailed subgroup of patients who may respond or not respond to antipsychotic treatment as early as possible after treatment commencement, focusing on trajectories of individual symptoms in the early stage of treatment.

The aim of the present study was to identify individual symptoms such as psychosis or aggression by which early improvements in scores on the NPI and BPRS at week 2 could predict subsequent treatment response of the overall NPSs to antipsychotics at week 8 in patients with AD.

METHODS

Study Design and Participants

In the present study, we used the CATIE-AD (ClinicalTrials.gov identifier: NCT00015548) phase 1 dataset, which is ideal given its detailed background information and inclusion of clinically defined AD among a clinic/research-based population.[6,13] The CATIE-AD study included patients with psychotic or aggressive symptoms who needed administration of atypical antipsychotics as a pharmacologic intervention for troubles in their daily life.[13] The CATIE-AD trial was performed between April 2001 and November 2004 at 45 sites in the United States.[6,13] All patients were diagnosed as having dementia of the Alzheimer's type according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV*), or probable AD based on the history, physical examination, and results of structural brain imaging.[6,13] All participants gave written informed consent to participate in the protocols approved by the local institutional review boards. Ethical approval was not sought for this specific analysis that used completely anonymous data. The severity of NPSs was evaluated with the NPI (score range, 0–120).[14] The severity of psychiatric symptoms including hallucinatory behavior, blunted affect, anxiety, and excitement in patients with AD was measured with the BPRS (score range, 0–108).[15] Both clinical scales were administered at baseline and weeks 2, 4, and 8, and information was gained from subjects (interview-based) or informants/caregivers who lived with the patients or visited the patients for at least 8 hours per week across at least 3 days per week.[13] Global cognitive function was evaluated with the Mini-Mental State Examination (MMSE) (score range, 0–30).[16] ADL were assessed with the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) (score range, 0–78).[17] General medical health was evaluated using the General Medical Health Rating (GMHR) (score range, 1–4).[18] A higher score reflects a better state for the ADCS-ADL, GMHR, and MMSE, while a higher score indicates a worse state for the BPRS and NPI. Baseline sociodemographic and clinical data including caregiver burdens were collected after the screening of eligibility for the study.[19] Trial medications (olanzapine: 2.5 mg or 5.0 mg, quetiapine: 25 mg or 50 mg, risperidone: 0.5 mg or 1.0 mg, or placebo) were randomly assigned to patients in phase 1. Medication dosage was adjusted by study physicians based on their clinical judgment and patient response.[13]

Early Improvements of NPSs at Week 2

The early improvement of NPSs was defined as changes in the total score and individual item scores from baseline to week 2 of the NPI and BPRS. The 10 individual NPI symptom items included in the study were as follows: (1) delusions, (2) hallucinations, (3) agitation, (4) depression, (5) anxiety, (6) euphoria/elation, (7) apathy, (8) disinhibition, (9) irritability, and (10) aberrant motor behavior.[14] The 18 individual symptoms evaluated by the BPRS were as follows: (1) somatic concern, (2) anxiety, (3) emotional withdrawal, (4) conceptual disorganization, (5) guilty mind, (6) tension, (7) mannerism and posturing, (8) grandiosity, (9) depressive mood, (10) hostility, (11) suspiciousness, (12) hallucinatory behavior, (13) motor retardation, (14) uncooperativeness, (15) unusual thought content, (16) blunted affect, (17) excitement, and (18) disorientation.[15] A score for each item ranges from 0 to 12 and from 0 to 6 on the NPI and BPRS, respectively. Moreover, we defined an "early improvement" in each item score change as follows: an item score reduction of $>0.5\times$ (standard deviation [SD] of each item score change at week 2), which is a minimal improvement difference (MID) score decided on per distribution-based methods.[20]

Definitions of Treatment Response at Week 8 as Outcomes

The treatment improvement in the present study represented a conventional "minimum improvement" in a longitudinal treatment course. We defined treatment response based on the established consensus or conventional MID score in previous studies as follows[7–9,20]: (1) a score reduction of ≥ 9 points from baseline at week 8 on the NPI calculated as MID score: $0.5\times$ (SD of the NPI total score change in the present study [17.9]), or 0 at endpoint when the baseline NPI total score was less than 9 points; and (2) reduction rate of $\geq 25\%$ in the BPRS total score from baseline.[7,20,21] The last-observation-carried-forward (LOCF) method was employed to evaluate each response outcome because the discontinuation rate at week 8 was about 50% in the dataset.[6]

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Table 1. Demographic and Clinical Data in Subjects at Baseline[a]

Variable	Value
Continuous	Mean ± SD (Range)
Age, y (n = 421)	77.9 ± 7.5 (51–103)
Education, y (n = 421)	12.3 ± 3.4 (0–21)
MMSE total score (n = 416)	15 ± 5.8 (4–29)
ADCS-ADL total score (n = 413)	39.0 ± 17.2 (2–76)
GMHR score (n = 420)	3.3 ± 0.7 (2–4)
Burden interview total score (n = 409)	34.4 ± 16.0 (0–76)
NPI total score	
Baseline (n = 414)	36.9 ± 18.3 (3–104)
Week 2 (n = 370)	30.2 ± 18.9 (0–100)
Week 8 (n = 386)[b]	29.0 ± 19.3 (0–100)
BPRS total score	
Baseline (n = 419)	27.8 ± 12.3 (3–72)
Week 2 (n = 372)	24.5 ± 12.3 (0–68)
Week 8 (n = 388)[b]	23.6 ± 12.3 (0–62)
Categorical	n (%)
Sex, female/male	235 (55.8)/186 (44.2)
Race, white/non-white	331(78.6)/88(20.9)
Present marital status, married/not	249 (59.1)/172 (40.9)
Residence, own home/not	307 (72.9)/114 (27.1)
Presence of past medical histories	
Diabetes mellitus	59 (14.0)
Cardiac disorders	118 (28.0)
Cerebrovascular accidents	43 (10.2)
Presence of concomitant medications at baseline	
Anticholinesterase	205 (48.7)
Psychotropic	136 (32.3)
Antipsychotic medications or placebo	
Olanzapine	100 (23.8)
Quetiapine	94 (22.3)
Risperidone	85 (20.2)
Placebo	142 (33.7)
NPI responder (reduction in total score ≥ 9 points)	
Week 2 (n = 368)	148 (40.2)
Week 8[b] (n = 383)	176 (46.0)
BPRS responder (reduction in total score ≥ 25%)	
Week 2 (n = 371)	105 (28.3)
Week 8[b] (n = 387)	145 (37.5)

[a]Total n = 421 unless otherwise noted.
[b]Each score or responder was evaluated by last-observation-carried-forward method at week 8.
Abbreviations: ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living, BPRS = Brief Psychiatric Rating Scale, GMHR = General Medical Health Rating, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory.

Table 2. NPI and BPRS Individual and Total Scores at Baseline and Week 2[a]

	Baseline	Week 2	Score Change[b]
Individual Symptom Scores on the NPI (range, 0–12)			
1. Delusions	5.5 ± 4.0	4.2 ± 3.8	−1.2 ± 3.7
2. Hallucinations	2.9 ± 3.7	2.3 ± 3.3	−0.6 ± 2.8
3. Agitation	5.5 ± 3.6	4.3 ± 3.7	−1.1 ± 3.7
4. Depression	2.7 ± 3.2	2.2 ± 3.0	−0.4 ± 3.2
5. Anxiety	3.8 ± 3.8	3.3 ± 3.6	−0.5 ± 3.6
6. Euphoria/elation	0.4 ± 1.4	0.3 ± 1.3	−0.1 ± 1.3
7. Apathy	4.3 ± 3.8	3.6 ± 3.8	−0.7 ± 3.8
8. Disinhibition	2.2 ± 3.3	1.9 ± 3.1	−0.2 ± 3.1
9. Irritability	5.1 ± 3.9	4.1 ± 3.7	−1.0 ± 3.8
10. Aberrant motor behavior	4.5 ± 4.4	4.0 ± 4.2	−0.5 ± 3.6
Total NPI score (range, 0–120)	36.9 ± 18.3	30.2 ± 18.9	−6.3 ± 15.7
Individual Symptom Scores on the BPRS (range, 0–6)			
1. Somatic concern	1.0 ± 1.4	0.8 ± 1.2	−0.2 ± 1.2
2. Anxiety	2.1 ± 1.6	1.9 ± 1.5	−0.2 ± 1.5
3. Emotional withdrawal	1.2 ± 1.3	1.0 ± 1.3	−0.2 ± 1.2
4. Conceptual disorganization	2.1 ± 1.6	1.9 ± 1.5	−0.2 ± 1.1
5. Guilty mind	0.4 ± 1.0	0.3 ± 0.8	−0.1 ± 0.9
6. Tension	1.6 ± 1.5	1.5 ± 1.4	0.0 ± 1.4
7. Mannerism and posturing	0.3 ± 0.8	0.2 ± 0.6	−0.1 ± 0.6
8. Grandiosity	0.4 ± 1.0	0.4 ± 0.9	0.0 ± 0.8
9. Depressive mood	1.5 ± 1.4	1.3 ± 1.4	−0.2 ± 1.2
10. Hostility	2.4 ± 1.7	2.1 ± 1.7	−0.3 ± 1.5
11. Suspiciousness	2.3 ± 1.7	1.9 ± 1.6	−0.4 ± 1.4
12. Hallucinatory behavior	1.7 ± 1.8	1.4 ± 1.7	−0.2 ± 1.4
13. Motor retardation	1.2 ± 1.4	1.0 ± 1.3	−0.1 ± 1.1
14. Uncooperativeness	1.9 ± 1.7	1.6 ± 1.6	−0.3 ± 1.3
15. Unusual thought content	2.1 ± 1.8	1.8 ± 1.7	−0.2 ± 1.5
16. Blunted affect	1.1 ± 1.4	1.0 ± 1.3	−0.1 ± 1.1
17. Excitement	1.4 ± 1.5	1.1 ± 1.3	−0.2 ± 1.2
18. Disorientation	3.3 ± 1.2	3.2 ± 1.2	−0.1 ± 1.0
Total BPRS score (range, 0–108)	27.8 ± 12.3	24.5 ± 12.4	−2.9 ± 8.7

[a]All values shown as mean ± SD.
[b]Score change = (total/individual symptom score at week 2) – (total/individual symptom score at baseline).
Abbreviations: BPRS = Brief Psychiatric Rating Scale, NPI = Neuropsychiatric Inventory.

Statistical Analysis

Multiple logistic regression model (stepwise forward selection) analyses were performed to examine factors associated with NPI treatment response at week 8 using early improvement in the NPI total and individual symptom score changes at week 2 ([score at week 2] – [score at baseline]).[22] The same analysis was conducted for the BPRS. In addition, the following factors at baseline were also added as confirmed independent variables based on previous reports of the CATIE-AD study[8]: (1) age; total scores on the MMSE, GMHR, and BPRS; history of diabetes mellitus; and treatment with risperidone at baseline for the analysis on the NPI and (2) age and total scores on the MMSE, GMHR, and BPRS at baseline for the analysis on the BPRS.[8] Nagelkerke R^2 values were calculated for the explained variation. We also examined the percentage accuracy in classification, which reflects the percentage of cases that can be correctly classified as nonresponder with the independent variables. Moreover, we calculated the number needed to treat (NNT) to evaluate how much each early non-improvement at week 2 (defined based on a MID score reduction) would contribute to treatment nonresponse at week 8. A P value $< .05$ was considered statistically significant (2-tailed), given that the present study set an a priori hypothesis that early improvement in individual NPI and BPRS item scores would predict treatment response in patients with AD who presented with NPSs. IBM SPSS Statistics Version 22.0 (IBM Corp; Armonk, New York) was used for the statistical analyses.

RESULTS

Patient Characteristics

Four hundred twenty-one patients with AD (235 women [55.8%]; mean ± SD age = 77.9 ± 7.5 years) were included in the present analysis. Clinicodemographic characteristics at baseline are depicted in Table 1. The percentages of the responders were 46.0% for NPI-defined responders and 37.5% for BPRS-defined responders. Table 2 depicts total and individual symptom scores on the BPRS and NPI at baseline and week 2 and the score changes from baseline to week 2.

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Table 3. Association of Early Improvements in Individual Symptoms in NPI and BPRS Responders at Week 8[a]

Variable	OR	*P* Value	95% CI	NNT (Range)	Other Values
NPI Responders[b]					
Euphoria/elation	0.77	.023*	0.59–0.96	5.23 (2.82–infinity)	
Irritability	0.87	.001**	0.80–0.94	2.65 (2.13–3.62)	
Hallucinations	0.87	.006**	0.79–0.96	4.03 (2.79–7.81)	
Anxiety	0.88	.002**	0.81–0.95	5.08 (3.28–12.6)	
Agitation	0.88	.003**	0.81–0.96	3.14 (2.42–4.60)	
Apathy	0.89	.002**	0.83–0.96	4.70 (3.17–9.55)	
Disinhibition	0.89	.014*	0.81–0.98	3.96 (2.75–7.71)	
Depression	0.90	.029*	0.83–0.99	3.91 (2.75–7.24)	
Nagelkerke R^2					0.39
PAC, %					76.1
BPRS Responders[c]					
Excitement	0.62	<.001***	0.49–0.79	3.35 (2.47–5.39)	
Suspiciousness	0.68	<.001***	0.55–0.83	3.17 (2.44–4.66)	
Disorientation	0.70	.014*	0.52–0.93	3.34 (2.45–5.41)	
Hostility	0.72	.001**	0.60–0.87	3.61 (2.67–5.73)	
Depressive mood	0.73	.006**	0.58–0.92	5.12 (3.27–12.12)	
Emotional withdrawal	0.76	.017*	0.60–0.95	5.81 (3.59–15.50)	
Nagelkerke R^2					0.34
PAC, %					74.9

[a]Logistic regression models (stepwise) were used.
[b]Response on the NPI was defined as a reduction ≥ 9 points at week 8. Age; scores on the MMSE, GMHR, and BPRS; history of diabetes mellitus; and treatment with risperidone at baseline were added to 10 NPI item score changes as independent variables in the regression model of NPI score responder.
[c]Response on the BPRS was defined as a reduction in total score ≥ 25% at week 8. Age and scores on the MMSE, GMHR, and BPRS at baseline were added to 18 BPRS item score changes as independent variables in the regression model of BPRS score responder.
*P < .05. **P < .01. ***P < .001.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, GMHR = General Medical Health Rating, MMSE = Mini-Mental State Examination, NNT = number needed to treat, NPI = Neuropsychiatric Inventory, OR = odds ratio, PAC = percentage accuracy in classification.

Prediction of Treatment Response at Week 8 Using Score Changes for Individual BPRS and NPI Symptoms at Week 2

Table 3 depicts the associations between clinical variables at baseline and score changes in each individual symptom at week 2 as well as subsequent treatment response per the NPI and BPRS, respectively, at week 8. For the NPI, the model explained 39% (Nagelkerke R^2) of the variance in treatment response and correctly classified 76.1% of the cases. Early improvements in euphoria/elation, irritability, hallucinations, anxiety, agitation, apathy, disinhibition, and depression contributed to a higher rate of treatment response. Likewise, the model for the BPRS explained 34% (Nagelkerke R^2) of the variance in treatment response and correctly classified 74.9% of the cases. Early improvements in excitement, suspiciousness, disorientation, hostility, depressive mood, and emotional withdrawal were associated with a higher rate of treatment response. Moreover, Table 3 depicts the NNT for each item of the NPI and BPRS. The numbers needed to treat for the NPI items were as follows: irritability (2.65), agitation (3.14), depression (3.91), disinhibition (3.96), hallucination (4.03), apathy (4.70), anxiety (5.08), and euphoria/elation (5.23). Numbers needed to treat for the BPRS items were as follows: suspiciousness (3.17), disorientation (3.34), excitement (3.35), hostility (3.61), emotional withdrawal (5.12), and depressive mood (5.81).

Prediction of Treatment Response at Week 8 Using Changes in NPI and BPRS Total Scores at Week 2

Table 4 depicts the associations between total score changes at week 2 and some clinical variables at baseline, and subsequent treatment response per the NPI and BPRS, respectively, at week 8. The model for the NPI explained 38% (Nagelkerke R^2) of the variance in treatment response and correctly classified 76.6% of the cases. Early improvement in NPI total scores was related to a higher rate of treatment response. Likewise, the model for the BPRS explained 33% (Nagelkerke R^2) of the variance in treatment response and correctly classified 73.8% of the cases. Early improvements in BPRS total scores and higher GMHR score at baseline significantly contributed to a higher rate of treatment response.

DISCUSSION

To the best of our knowledge, this study is the first to investigate individual symptoms whose early improvements with atypical antipsychotics at week 2 could predict subsequent treatment response at week 8 after initiation of antipsychotics in patients with AD who presented with NPSs. According to odds ratios in the conceptual model, the main results of this study were as follows: in patients with AD who presented with NPSs, (1) early improvement

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Table 4. Association of Early Improvements in Total Symptoms in NPI and BPRS Responders at Week 8[a]

Variable	OR	*P* Value	95% CI	Other Values
NPI Responders[b]				
NPI total score change	0.90	<.001***	0.88–0.92	
Nagelkerke R^2				0.38
PAC, %				76.6
BPRS Responders[c]				
BPRS total score change	0.85	<.001***	0.82–0.89	
GMHR score at baseline	1.50	.034*	1.03–2.18	
Nagelkerke R^2				0.33
PAC, %				73.8

[a]Logistic regression models (stepwise) were used.
[b]Response on the NPI was defined as a reduction ≥ 9 points at week 8. Age; scores on the MMSE, GMHR, and BPRS; history of diabetes mellitus; and treatment with risperidone at baseline were added to NPI total score change as independent variables in the regression model for NPI score responders.
[c]Response on the BPRS was defined as a reduction in total score ≥ 25% at week 8. Age and scores on the MMSE, GMHR, and BPRS at baseline were added to BPRS total score changes as independent variables in the regression model for BPRS score responders.
*P < .05. ***P < .001.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, GMHR = General Medical Health Rating, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, OR = odds ratio, PAC = percentage accuracy in classification.

in euphoria/elation, irritability, hallucinations, anxiety, agitation, apathy, disinhibition, and depression as assessed by the NPI was related to subsequent treatment response; (2) early improvement in excitement, suspiciousness, disorientation, hostility, depressive mood, and emotional withdrawal as assessed by the BPRS was associated with treatment response; and (3) healthier condition at baseline was also related to treatment response.

A previous study[11,12] demonstrated that early improvements on positive symptom items of the Positive and Negative Syndrome Scale (PANSS) were associated with long-term treatment response in patients with schizophrenia. Moreover, using 2 symptomatic factors (ie, [1] thought disturbance: hallucinatory behavior, unusual thought content, and conceptual disorganization; and [2] hostility-suspicious: hostility, suspiciousness, and uncooperativeness) on the BPRS, another study[10] indicated that early improvements of positive symptoms were more robustly related to treatment response than were anxiety/depression or withdrawal/retardation factors in patients with schizophrenia. These findings emphasized the importance of careful monitoring of positive symptoms to predict subsequent treatment outcomes in patients with schizophrenia.[10] In the present study, early improvement in so-called positive symptoms (suspiciousness, hostility, or hallucinations) was related to subsequent treatment response in patients with AD, which is consistent with previous studies on the treatment of schizophrenia.[10–12] Next, early improvement in aggressiveness symptoms (excitement, irritability, or agitation) also contributed to subsequent treatment response of the overall NPSs. Ruberg et al[12] reported that early changes (at week 2) on the excitement item of the PANSS predicted long-term treatment response to atypical antipsychotics in patients with chronic schizophrenia. Therefore, these findings indicate that it may be important to focus on the early changes in aggressive affect in patients with AD when treating psychotic or aggressive symptoms with atypical antipsychotics. Moreover, among NPI items, early improvement of euphoria/elation and disinhibition predicted subsequent treatment response of the overall NPSs. Previously,[23] we classified the 12 NPI items in patients participating in the CATIE-AD trial into 4 subgroups by principal component analysis. We found that these 2 symptoms were classified in the same subgroup: the emotion and disinhibition cluster.[23] A recent study[24] also demonstrated that euphoria/elated affect was associated with severe agitation in patients with dementia. Therefore, early improvement of euphoria/elation or disinhibition may contribute to the improvement of agitation in patients with AD, which may, in turn, lead to whole treatment response for NPSs overall.

In contrast, we found that early improvements in a wide range of symptoms were related to subsequent treatment response in patients with AD presenting with NPSs. Disorientation score among BPRS items reflects comprehension of time and place and correct person identification.[15] Previous studies noted that neurocognitive preservation was related to subsequent NPS improvement/prevention,[25,26] supporting our result that early improvement of disorientation contributed to later treatment response. Moreover, early improvement of symptoms other than positive symptoms such as depressive mood and emotional withdrawal was also associated with subsequent treatment response. While there are pharmacologic interventions to clearly improve psychosis and aggressive symptoms, non-pharmacologic interventions for patients and their caregivers might have also improved their depressive mood or emotional withdrawal, which may, in turn, decrease overall NPS severity.[27–29] When treating NPSs with antipsychotics, which target psychosis or aggression, clinicians may also need to pay attention to motivational and emotional problems and monitor early cognitive declines.

To the best of our knowledge, only 1 study to date has investigated whether early improvements in individual symptoms could predict subsequent response to antipsychotics in patients with schizophrenia. In that study, Ruberg et al[12] reported that early changes in individual positive symptoms could predict long-term response to atypical antipsychotics in the treatment of schizophrenia. The evaluation of clinical severity by a total score rather than measurable individual scores is considered to be one of the limitations in modern psychiatry. Given limited time in clinical practice, further research is needed to detect individual symptoms whose improvements can predict subsequent response for each patient with schizophrenia.

When ranking these significant early non-improvements of individual items according to contribution to subsequent treatment outcomes, we compared each NNT score for the individual items (Table 3). In terms of the individual symptom items on the NPI, non-improvement in irritability (NNT = 2.65) at week 2 was the strongest predictor of

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treatment nonresponse compared with the other individual symptoms. With regard to the individual symptom items on the BPRS, early non-improvement in suspiciousness (NNT = 3.17) at week 2 was more strongly associated with nonresponse than the other items. These results are in line with those of previous studies[10,12] of schizophrenia which reported that non-improvement in excitement and positive symptom domains were related to treatment nonresponse based on the BPRS. Therefore, these results suggest that, in an effort to avoid unnecessary adverse events, it would be beneficial to more carefully monitor irritability and suspiciousness in patients with AD whose NPSs are required to be treated with atypical antipsychotics.

Besides the early improvement in total score of the NPSs, healthier status at baseline was associated with treatment response on the BPRS in the present study (Table 4). The finding is in line with those of previous studies[30,31] which noted that healthier status is a protective factor against NPSs in this patient population.

Limitations

The present study has several limitations. First, the discontinuation rate at week 8 was about 50%, which is higher than in studies evaluating atypical antipsychotic treatment response.[10–12,22] Therefore, the LOCF method was employed to evaluate a treatment response outcome. Second, subsequent treatment response was defined based on previous studies.[7–9,20] Although the consensus of those definitions is confirmed, an appropriate interpretation of the results may be required. Third, the influence of medication dosage was not taken into account since flexible dosing was employed in the original CATIE-AD study.[13] Fourth, the antidepressant or anticonvulsant effectiveness for overall NPSs has been shown in a recent systematic review,[28] but we did not include concomitant medications (ie, psychotropics, anticholinesterase drugs, or antihypertensive drugs) prior to the trial initiation as confounding factors in the present study. Although they may have influence as clinical predictors of subsequent response, we found no relationship between concomitant medications and subsequent treatment response in the previous reports of the CATIE-AD study.[8] Fifth, the NPI consists of 12 individual items (eg, psychosis/aggressiveness and apathy/depressive), individual item scores of which were reported to be correlated among each other.[23] Moreover, even if total NPI scores are the same for different patients, the severity or frequency of individual symptoms may be different. The NPI has a structural limitation in that NPI total score reflects the sum of the 12 items with disregard to detailed contents. Therefore, the treatment response as defined by NPI total score in the present study reflects only a change in the overall NPS severity. Sixth, although hallucinations and anxiety as noted by NPI item scores significantly contributed to subsequent treatment response, we did not find significant contributions of the same symptom items on the BPRS. While NPI item score (range, 0–12) is described by a product of its disease severity score (range, 0–3) and frequency score (range, 0–4), BPRS item score is based only on severity. Therefore, this difference in evaluation structure between the two scales might at least in part contribute to the discrepancy. For these reasons, our results should be viewed as preliminary findings that warrant a further prospective clinical study to confirm our observations.

Conclusion

In conclusion, early improvements of several individual symptoms at week 2 might contribute to treatment response at week 8 in AD patients with NPSs. Given that it may be difficult to examine all of the clinical symptoms to assess overall symptom severity in daily clinical practice, focusing on specific early improvements of individual symptoms (ie, irritability and suspiciousness) during the course of treatment with antipsychotics may help predict patients' subsequent treatment outcomes. Ultimately, this prediction will lead to the prevention of excessive exposure to antipsychotics that are unlikely to have a beneficial impact on patients. Although our preliminary findings warrant further research to validate them, the current results suggest that focusing on trajectories of the emotional, motivational, and cognitive domains as well as the positive symptomatic domain would be helpful for clinicians to judge risk and benefit as early as possible to determine whether continuing the current antipsychotics is the best course; doing so would eventually lead to the patient's benefit.

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REFERENCES

1. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939–944.
2. de Vugt ME, Stevens F, Aalten P, et al. A prospective study of the effects of behavioral symptoms on the institutionalization of patients with dementia. *Int Psychogeriatr*. 2005;17(4):577–589.
3. Ballard CG, Gauthier S, Cummings JL, et al. Management of agitation and aggression associated with Alzheimer disease. *Nat Rev Neurol*. 2009;5(5):245–255.
4. Herrmann N, Gauthier S, Lysy PG. Clinical practice guidelines for severe Alzheimer's disease. *Alzheimers Dement*. 2007;3(4):385–397.
5. Yunusa I, Alsumali A, Garba AE, et al. Assessment of reported comparative effectiveness and safety of atypical antipsychotics in the treatment of behavioral and psychological symptoms of dementia: a network meta-analysis. *JAMA Netw Open*. 2019;2(3):e190828.
6. Schneider LS, Tariot PN, Dagerman KS, et al; CATIE-AD Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*. 2006;355(15):1525–1538.
7. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;366(10):893–903.
8. Nagata T, Nakajima S, Shinagawa S, et al. Baseline predictors of antipsychotic treatment continuation and response at week 8 in patients with Alzheimer's disease with psychosis or aggressive symptoms: an analysis of the CATIE-AD Study. *J Alzheimers Dis*. 2017;60(1):263–272.
9. Ozawa C, Roberts R, Yoshida K, et al. Placebo effects in the treatment of noncognitive symptoms of Alzheimer's disease: analysis of the CATIE-AD Data. *J Clin Psychiatry*. 2017;78(9):e1204–e1210.
10. Correll CU, Malhotra AK, Kaushik S, et al. Early prediction of antipsychotic response in schizophrenia. *Am J Psychiatry*. 2003;160(11):2063–2065.
11. Kinon BJ, Chen L, Ascher-Svanum H, et al. Predicting response to atypical antipsychotics based on early response in the treatment of schizophrenia. *Schizophr Res*. 2008;102(1–3):230–240.
12. Ruberg SJ, Chen L, Stauffer V, et al. Identification of early changes in specific symptoms that predict longer-term response to atypical antipsychotics in the treatment of patients with schizophrenia. *BMC Psychiatry*. 2011;11(1):23.
13. Schneider LS, Tariot PN, Lyketsos CG, et al. National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer disease trial methodology. *Am J Geriatr Psychiatry*. 2001;9(4):346–360.
14. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology*. 1997;48(suppl 6):S10–S16.
15. Beller SA, Overall JE. The Brief Psychiatric Rating Scale (BPRS) in geropsychiatric research, II: representative profile patterns. *J Gerontol*. 1984;39(2):194–200.
16. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state:" a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
17. Galasko D, Bennett D, Sano S, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease: the Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11(suppl 2):S33–S39.
18. Lyketsos CG, Galik E, Steele C, et al. The General Medical Health Rating: a bedside global rating of medical comorbidity in patients with dementia. *J Am Geriatr Soc*. 1999;47(4):487–491.
19. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist*. 1980;20(6):649–655.
20. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. 2003;41(5):582–592.
21. Leucht S, Kane JM, Etschel E, et al. Linking the PANSS, BPRS, and CGI: clinical implications. *Neuropsychopharmacology*. 2006;31(10):2318–2325.
22. Jakubovski E, Carlson JP, Bloch MH. Prognostic subgroups for remission, response, and treatment continuation in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial. *J Clin Psychiatry*. 2015;76(11):1535–1545.
23. Nagata T, Shinagawa S, Nakajima S, et al. Classification of neuropsychiatric symptoms requiring antipsychotic treatment in patients with Alzheimer's disease: analysis of the CATIE-AD Study. *J Alzheimers Dis*. 2016;50(3):839–845.
24. Palm R, Sorg CGG, Ströbel A, et al. Severe agitation in dementia: an explorative secondary data analysis on the prevalence and associated factors in nursing home residents. *J Alzheimers Dis*. 2018;66(4):1463–1470.
25. Nagata T, Shinagawa S, Nakajima S, et al. Association between neuropsychiatric improvement and neurocognitive change in Alzheimer's disease: analysis of the CATIE-AD Study. *J Alzheimers Dis*. 2018;66(1):139–148.
26. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *Am J Psychiatry*. 2005;162(11):2022–2030.
27. Theleritis C, Siarkos K, Politis AA, et al. A systematic review of non-pharmacological treatments for apathy in dementia. *Int J Geriatr Psychiatry*. 2018;33(2):e177–e192.
28. Dyer SM, Harrison SL, Laver K, et al. An overview of systematic reviews of pharmacological and non-pharmacological interventions for the treatment of behavioral and psychological symptoms of dementia. *Int Psychogeriatr*. 2018;30(3):295–309.
29. Kubo Y, Hayashi H, Kozawa S, et al. Relevant factors of depression in dementia modifiable by non-pharmacotherapy: a systematic review. *Psychogeriatrics*. 2019;19(2):181–191.
30. Steinberg M, Corcoran C, Tschanz JT, et al. Risk factors for neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry*. 2006;21(9):824–830.
31. Treiber KA, Lyketsos CG, Corcoran C, et al. Vascular factors and risk for neuropsychiatric symptoms in Alzheimer's disease: the Cache County Study. *Int Psychogeriatr*. 2008;20(3):538–553.

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