Early Prediction of Clinical Response in Schizophrenia Patients Receiving the Atypical Antipsychotic Zotepine

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Objective: Prior early prediction models for antipsychotic treatment response demonstrate good specificity but poor sensitivity (i.e., high false-negative rates). The purpose of this study was to refine the early prediction model in schizophrenia patients taking an atypical antipsychotic agent, zotepine.

Method: 135 acutely ill inpatients with DSM-IV–defined schizophrenia received 4 weeks of 150 mg/day zotepine treatment. Psychopathology severity was assessed weekly with the Brief Psychiatric Rating Scale (BPRS) and subscales for positive, negative, and general symptoms. Clinical response was defined as a reduction of 20% or more in the BPRS total score at week 4. A logistic regression model was used to obtain early predictors. The receiver operating characteristic curve was employed to determine the optimal cutoff points of the variables for predicting response. The study was conducted from June 2004 to April 2005.

Results: The most significant early predictors for ultimate response at week 4 were BPRS positive subscale score changes at week 1 and, better, at week 2 ($p < .001$ at both timepoints). At week 1, a BPRS positive score reduction of 4 appeared to be the optimal cutoff point for predicting eventual response, providing a sensitivity of 0.77 and specificity of 0.77. At week 2, a BPRS positive score reduction of 6 was the best for prediction, with a sensitivity of 0.83 and specificity of 0.91.

Conclusions: These findings suggest that using the first 2 weeks' improvement in positive symptoms to predict the fourth week's treatment response is favorable in terms of both specificity and sensitivity. Further studies are needed. Moreover, whether this model could be applied to establish a prediction system for other antipsychotics or other psychotropics also deserves research.

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Treatment guidelines, such as the American Psychiatric Association's Practice Guideline for the Treatment of Patients With Schizophrenia,[1] recommend that clinicians should monitor antipsychotic response for at least 3 to 4 weeks before increasing the dose or changing medications. Early identification of nonresponders to antipsychotics could prevent unnecessary persistence with ineffectual agents, diminish risk of adverse events, decrease duration of hospitalization, and reduce illness cost and burden.

Studies investigating clinical and biological response predictors in schizophrenia have yielded inconsistent results, and methodological differences limit the interpretation of these data.[2–4] The studies examining the correlation between early therapeutic changes and eventual antipsychotic response have yielded positive results.[2,5–10] However, interpretation of these studies is restricted by small sample sizes (up to 72 subjects), inclusion of a majority of nonresponders,[2] exclusion of female[2] or male[7] patients, nonstandardized treatment,[5,8,10] trial durations of as little as 2[5] or 3[8] weeks, unusual loading strategies,[2,9] and heterogeneous, nonoperationalized predictor and outcome variables.[2,5,7,10]

Correll et al.[11] recently used early symptom reduction at week 1 to predict the endpoint (week 4) treatment response, defined as a reduction of 20% or more in Brief

Psychiatric Rating Scale (BPRS)[12] total score, in 131 acutely ill schizophrenic or schizoaffective inpatients who received fixed-dose, 20-mg/day, therapy with fluphenazine, a first-generation antipsychotic agent. They found that 100% of patients who displayed an improvement of less than 20% in BPRS total score and 95% of patients who displayed a reduction of less than 20% in BPRS thought disturbance factor score following 1 week of treatment turned out to be nonresponders after 4 weeks of treatment. That is, the specificities for the nonresponse prediction were very high (100% and 95%), suggesting that treatment resistance may already be identifiable after 1 week. However, the corresponding sensitivities were very low (35% and 53%): ≥ 20% reductions in the total BPRS and thought disturbance factor scores at 1 week correctly identified response in only 35% and 53% of patients, respectively. In other words, the false-negative rates were very high. The predictive power values were 63% and 71%, respectively. Correll et al.[11] also suggested that further studies, preferably involving second-generation antipsychotics (also called atypical antipsychotics), are needed to better determine the predictive value of initial symptom reductions for ultimate treatment response.

A meta-analytic study[13] indicated that (1) clinical improvement during the first week of antipsychotic treatment is greater than that observed in the subsequent 3 weeks and (2) greater improvement also occurs in the first 2 weeks than in the subsequent 2 weeks. To increase the sensitivity (or, equivalently, to reduce the false-negative rate) of the prediction model, the current study applied early symptom reductions at both week 1 and week 2 to predict eventual response at week 4 in schizophrenia patients using zotepine, an atypical antipsychotic agent commonly used in some European countries, Japan, and Taiwan.

METHOD

This study was conducted in the inpatient unit of Kai-Suan Psychiatry Hospital (a major psychiatric center in Taiwan), Kaohsiung. The study was approved by the facility's institutional review board and conducted in accordance with the Declaration of Helsinki. The study was conducted from June 2004 to April 2005.

Subjects

All newly hospitalized schizophrenic patients with acute exacerbation were screened and evaluated by the research psychiatrists. The Structured Clinical Interview for DSM-IV[14] was conducted for the diagnosis. Han Chinese patients in Taiwan entered into this study if they (1) were physically healthy and had all laboratory parameters within normal limits, (2) were aged 18–65 years, (3) satisfied DSM-IV criteria for schizophrenia, (4) were rated as moderate or worse on at least 1 of the 4 BPRS psychotic symptom items (i.e., hallucinations, unusual thoughts, conceptual disorganization, or suspiciousness), (5) had no DSM-IV diagnosis of substance (including alcohol) abuse, (6) had not received depot antipsychotics for the preceding 3 months, and (7) gave written informed consent after the procedures had been fully explained. Patients were excluded from the study if they had a history of severe adverse reaction to antipsychotics or if they had been diagnosed with treatment-resistant schizophrenia.[15]

Procedures

After a washout period of at least 72 hours, patients received open-label zotepine treatment at a fixed dose of 150 mg daily for 4 weeks. Benzodiazepine was allowed as needed for insomnia or agitation, and trihexyphenidyl was allowed for extrapyramidal side effects. No other psychotropic agents were used.

Symptom severity was assessed weekly by trained and experienced psychiatrists using the 18-item BPRS, with scores ranging from 1 (symptoms not present) to 7 (extremely severe symptoms). BPRS contains 3 clusters, positive, negative, and general symptoms, according to the pivotal clozapine trial.[15] The positive cluster consists of 8 items: conceptual disorganization, mannerisms and posturing, grandiosity, hostility, suspiciousness, hallucinatory behavior, unusual thought content, and excitement. The negative cluster consists of 5 items: emotional withdrawal, motor retardation, uncooperativeness, blunted affect, and disorientation. The general cluster consists of 5 items: somatic concern, anxiety, guilt feelings, tension, and depressive mood.[15] Interrater reliability was established prior to the study with a κ score of 0.90. Clinical response was defined as a reduction of 20% or more in BPRS total score following 4 weeks of treatment. The research psychiatrists who conducted the clinical ratings did not know the detailed study design or the responder versus nonresponder status of patients as defined at weeks 1 and 2 during the study. Side effects were evaluated by the UKU Side Effect Rating Scale,[16] with scores ranging from 0 (none) to 3 (severe).

Statistical Analyses

Initially, responders and nonresponders at week 4 were compared in terms of demographic data (gender, age), age at illness onset, baseline BPRS total score, and BPRS total and cluster score changes at week 1 and week 2. Age at illness onset was regarded as age at the first psychotic symptom. Pearson χ^2 test or Fisher exact test was used to compare categorical variables; independent t test was used for continuous variables.

Second, if multiple potential predictive variables were identified from the first step, forward stepwise logistic regression model was employed to determine the best predictor for clinical response.

Finally, receiver operating characteristic (ROC) curve was used to determine the cutoff point of predictor

between the responders and nonresponders and to obtain the area under the ROC curve (AUC). ROC curve is a way to analyze the accuracy of diagnostic tests and to determine the best threshold or "cutoff" value for distinguishing between positive and negative test results. Diagnostic testing is almost always a "compromise" between sensitivity and specificity. ROC curve provides a graphic representation of the proportion of true-positive results (sensitivity) versus the proportion of false-positive results (1 – specificity).

All tests were 2-tailed, and significance was defined as an α of less than .05. We also used 95% confidence intervals (CIs) to indicate the precision of the odds ratios. Data were analyzed with SPSS version 10.0 for Windows (SPSS Inc.; Chicago, Ill.).

Table 1. Clinical Characteristics and BPRS Score Changes at Weeks 1 and 2 Between Zotepine Responders and Nonresponders Following 4 Weeks of Treatment

	Responders[a] (N = 78)		Nonresponders (N = 22)		Analysis		
Variable	N	%	N	%	χ^2	df	p
Male	40	51.3	14	63.6			
Female	38	48.7	8	36.4	1.05	1	.304
	Mean	SD	Mean	SD	t	df	p
Age, y	36.7	8.4	39.3	11.0	–1.17	98	.244
Age at illness onset, y	23.8	6.6	22.4	5.1	0.95	98	.344
Baseline BPRS total score	56.4	10.3	53.0	11.4	1.36	98	.176
BPRS score changes at week 1							
Total score	12.7	9.2	3.6	7.2	4.30	98	< .001
Positive symptoms	9.0	6.4	2.2	4.4	4.66	98	< .001
Negative symptoms	2.2	4.1	1.4	2.5	0.909	98	.366
General symptoms	1.6	2.8	0.0	3.2	2.21	98	.029
BPRS score changes at week 2							
Total score	17.2	9.1	4.5	7.0	6.08	98	< .001
Positive symptoms	11.7	6.5	2.4	3.7	6.40	98	< .001
Negative symptoms	3.5	4.4	1.9	3.1	1.58	98	.117
General symptoms	2.0	3.2	0.2	3.3	2.40	98	.018

[a]Patients with 20% or more reduction in the BPRS total score.
Abbreviation: BPRS = Brief Psychiatric Rating Scale.

RESULTS

A total of 135 acutely ill inpatients with schizophrenia were enrolled. One hundred (74.1%) of them completed the 4-week trial. The remaining 35 did not: 13 patients discharged from the hospital before week 4 due to uncooperativeness, 10 patients received haloperidol IM or increased dosage of zotepine to control agitation, and 12 patients did not tolerate the side effects of dizziness (N = 7), sleepiness (N = 3), and asthenia (N = 2). The dropout patients (N = 35) and the completers (N = 100) were comparable for gender (17 men/18 women vs. 54 men/46 women; $\chi^2 = 0.31$, df = 1, p = .580), age (36.7 ± 9.2 vs. 37.3 ± 9.1; t = –0.33, df = 133, p = .740), age at illness onset (24.9 ± 6.9 vs. 23.5 ± 6.4; t = 1.11, df = 133, p = .270), and baseline BPRS total score (56.6 ± 11.3 vs. 55.7 ± 10.6; t = 0.44, df = 133, p = .658).

Of the 100 completers, 78 patients (78%) met response criteria at week 4. Nonresponders were more likely to experience increased salivation (18.2% vs. 2.6%, p = .020) and rigidity (13.6% vs. 0%, p = .010) with 2-tailed Fisher exact tests. Frequencies of other side effects were comparable between responders and nonresponders (data not shown). No severe adverse events were found in any patient.

Table 1 displays a comparison of clinical characteristics and early BPRS score changes between the ultimate responders and nonresponders. There were no significant between-group differences with respect to sex, age, age at onset, or baseline BPRS total score. After 1 week and 2 weeks of treatment, changes in BPRS positive, general, and total scores were larger in the eventual responder group than in the nonresponder group.

Table 2. Early Predictors at Weeks 1 and 2 for Response (≥ 20% reduction in BPRS total score) at Week 4: Analyzed by Forward Stepwise Logistic Regression Model Using Changes in BPRS Total, Positive Symptom, and General Symptom Scores as Predicting Variables

Predictor	B	Odds Ratio[a]	95% CI	p
BPRS positive symptom score change at week 1	0.223	1.250	1.116 to 1.401	< .001
BPRS positive symptom score change at week 2	0.295	1.343	1.180 to 1.527	< .001

[a]Odds ratio(= Exp(B)): ratio of odds of response versus nonresponse.
Abbreviation: BPRS = Brief Psychiatric Rating Scale.

Since several potential predictive variables (changes in BPRS total, positive, and general scores) emerged (Table 1), we then applied a forward stepwise logistic regression model and found BPRS positive-symptom score changes at weeks 1 and 2 to be the most influential predictors for endpoint response (Table 2).

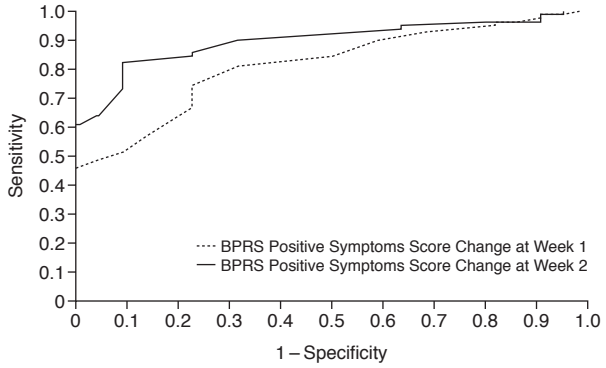
Finally, ROC analysis was employed to determine the cutoff point of score change as the predictor by plotting the proportion of true-positive results (sensitivity) versus the proportion of false-positive results (1 – specificity) (Table 3). At week 1, BPRS-positive score reduction of 4 appeared to be the optimal cutoff point for predicting eventual response, providing a sensitivity of 0.77, specificity of 0.77, and predictive power of 0.77. At week 2, a BPRS-positive score reduction of 6 was the best for prediction, with a sensitivity of 0.83, specificity of 0.91, and

Table 3. Prediction of Response (≥ 20% reduction in BPRS total score) at Week 4 Using BPRS Positive Symptom Score Change at Weeks 1 and 2: ROC Analysis[a]

Predictor	Score Reduction Used as Cutoff for Response	Sensitivity	Specificity	Predictive Power	Area Under ROC Curve
BPRS positive symptom score change at week 1	4	0.77	0.77	0.77	0.81
BPRS positive symptom score change at week 2	6	0.83	0.91	0.85	0.90

[a]For determining the cutoff point of score change as the predictor by plotting the proportion of true-positive results (sensitivity) versus the proportion of false-positive results (1 – specificity).
Abbreviations: BPRS = Brief Psychiatric Rating Scale, ROC = receiver operating characteristic.

Figure 1. ROC Curve for Zotepine Responders Versus Nonresponders at Week 1 and Week 2



Abbreviations: BPRS = Brief Psychiatric Rating Scale, ROC = receiver operating characteristic.

predictive power of 0.85. ROC curves at week 1 and week 2 are presented in Figure 1.

DISCUSSION

The main finding of this study is that BPRS positive subscale score reduction by ≥ 4 points at week 1 and ≥ 6 points at week 2 correctly identified ultimate response at the end of the study in 77% and 83% of patients, respectively. On the other hand, 77% of patients who displayed a < 4-point reduction in the BPRS-positive cluster at week 1 and 91% of patients with a < 6-point reduction in the BPRS-positive at week 2 were correctly identified as ultimate nonresponders. These findings suggest that improvement in positive symptoms at week 2 may be a better early predictor than that at week 1. Zotepine, as an atypical antipsychotic agent, is effective for both positive and negative symptoms; however, improvement in the negative symptoms is slower and relatively smaller than for that in positive symptoms, particularly in the acutely ill patients.[17,18] Accordingly, in the current study, early improvement in negative symptoms was not related with final response (Table 1).

The current study offered an advantage: ROC curve was applied to determine the cutoff point for early prediction of eventual response to obtain the highest sensitivity and specificity. Other strengths of this study include the use of structured instruments for diagnosis (Structured Clinical Interview for DSM-IV) and use of operationalized predictors as well as outcome variables.

Certainly, the findings in this study should be interpreted with caution. First, the nonblinded design impaired objectivity of the observers and patients, yet all patients received the same fixed-dose treatment. Second, like the limitations in the study of Correll et al.,[11] the trial duration of 4 weeks leaves the possibility that some patients may have responded had the trial lasted longer. However, studies[19,20] suggest that the majority of patients with schizophrenia achieve the plateau of clinical improvement within 4 weeks of acute treatment. Third, this study had a dropout rate of 25.9%, quite similar to that (27.5%) of the Correll et al. study,[11] yet the dropout patients did not differ from the completers in terms of demographic data or baseline illness severity. Finally, similar to the design of the Correll et al. study,[11] the patients in the current study received the same fixed dose, 150 mg daily, of zotepine treatment. This dosage, based upon previous studies in Western patients[21] and in Taiwanese,[22] is the optimal dose for treatment of schizophrenia. Moreover, schizophrenia patients taking 150 mg daily of zotepine reveal a striatal D_2 receptor occupancy of 65.8% (SD = 6.2),[23] and a brain imaging study indicates that D_2 receptor occupancy of 65% to 70% is correlated with maximal antipsychotic efficacy.[24] Certainly, it remains possible that a portion of patients require other doses of zotepine to reach clinical response.

In addition, other empirically derived factor scores for BPRS could also be applied. For example, Headlund and Vieweg[25] raised 4 factors: thought disturbance (hallucinations, unusual thoughts, conceptual disorganization), hostility-suspiciousness (hostility, suspiciousness, uncooperativeness), anxiety-depression (somatic concerns, anxiety, guilt feelings, depressed mood), and withdrawal-retardation (emotional withdrawal, psychomotor retardation, blunted affect). Analyzed with these clusters, the early score change of the BPRS total, rather than any of the factors, better predicted endpoint response (data not shown). Using ROC analysis, BPRS total score reduction of 10 at week 1 appeared to be the optimal cutoff point for predicting eventual response, with sensitivity of 0.62 and specificity of 0.82. At week 2, a BPRS total score

reduction of 13 was the best for prediction (sensitivity = 0.71, specificity = 0.91). This result, albeit not as good as that from the prediction method using early score reduction of the positive-symptom cluster (illustrated above), still supports that the current strategy could provide a relatively balanced model between specificity and sensitivity when compared to the previous prediction model without ROC analysis.[11]

In addition to 20%,[11,15,26] 30%[27,28] and other percentages[20,29–31] of the BPRS score reduction have been used to define response. If other cutoff values, e.g., 15% and 30%, were chosen for prediction, similar results were obtained using the model mentioned in the Method (data not shown).

The BPRS can be scaled in 2 ways: 1 to 7 (see Method and Results) or 0 to 6.[25] If assessed using BPRS with the 0-to-6 scaling system, 84 patients (84%) met response criteria at week 4. The BPRS positive symptom score changes at weeks 1 and 2 remained the most influential predictors for endpoint response (data not shown). At week 1, BPRS positive symptom score reduction of 3 appeared to be the optimal cutoff point for predicting eventual response (sensitivity = 0.82, specificity = 0.81). At week 2, BPRS positive symptom score reduction of 6 was the best for prediction (sensitivity = 0.82, specificity = 0.94).

Besides, BPRS focuses more on positive symptoms than on negative symptoms. There are other outcome measures available for schizophrenia, including the Positive and Negative Syndrome Scale[32] and Scale for the Assessment of Negative Symptoms,[33] as well as scales assessing quality of life,[34] social function (Nurses' Observation Scale for Inpatients Evaluation),[35,36] and neurocognitive functions.[37,38] Theoretically, they all can be treated as the response variable to establish an early prediction model.

Although this was a fixed-dose study, the results could provide a basis for further studies to develop an algorithm that might, for example, involve giving an average-sized dose for 1 week, then in the case of poor response increasing the dose for 1 week, and then in the case of ongoing poor response, switching to a new medication and repeating the steps. Further studies, preferably involving other atypical antipsychotics, larger patient groups, frequent early symptom ratings, and duration longer than 4 weeks, are needed to better determine the predictive value of initial symptom reductions for ultimate treatment response. Moreover, whether this model could be applied to establish a prediction system for other psychotropics, such as antidepressants, also deserves research.

Drug names: clozapine (FazaClo and others), fluphenazine (Prolixin and others)

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