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CLINICAL TRIAL STUDY

Early Efficacy of Antipsychotic Medications at Week 2 Predicts Subsequent Responses at Week 6 in a Large-scale Randomized Controlled Trial

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Abstract: ***Background*:** Since the early clinical efficacy of antipsychotics has not yet been well perceived, this study sought to decide whether the efficacy of antipsychotics at week 2 can predict subsequent responses at week 6 and identify how such predictive capacities vary among different antipsychotics and psychotic symptoms.

Methods: A total of 3010 patients with schizophrenia enrolled in a randomized controlled trial (RCT) and received a 6-week treatment with one antipsychotic drug randomly chosen from five atypical antipsychotics (risperidone 2-6 mg/d, olanzapine 5-20 mg/d, quetiapine 400-750 mg/d, aripiprazole 10-30 mg/d, and ziprasidone 80-160 mg/d) and two typical antipsychotics (perphenazine 20-60 mg/d and haloperidol 6-20 mg/d). Early efficacy was defined as the reduction rate using the Positive and Negative Syndrome Scale (PANSS) total score at week 2. With cut-offs at 50% reduction, logistic regression, receiver operating characteristic (ROC) and random forests were adopted.

***Results*:** The reduction rate of PANSS total score and improvement of psychotic symptoms at week 2 enabled subsequent responses to 7 antipsychotics to be predicted, in which improvements in delusions, lack of judgment and insight, unusual thought content, and suspiciousness/ persecution were endowed with the greatest weight.

***Conclusion*:** It is robust enough to clinically predict treatment responses to antipsychotics at week 6 using the reduction rate of PANSS total score and symptom relief at week 2. Psychiatric clinicians had better determine whether to switch the treatment plan by the first 2 weeks.

Clinical Trial Registration Number: This RCT was registered at the Chinese Clinical Trials Registry Identifier: ChiCTR-TRC-10000934).

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1. INTRODUCTION

The treatment of schizophrenia remains a major ongoing challenge for psychiatry. Currently, the prescription of antipsychotic medications is largely based on clinicians' judgment. Treatment guidelines are not always consistent, and there is a lack of consensus on how much time should elapse before the lack of response to treatment can be confirmed. For example, 4-6 weeks has been recommended by the British Association of Psychopharmacology and the National Institute of Clinical Excellence. It is generally accepted that there is a certain time lag between the administration of antipsychotic medications and a noticeable impact exerted upon symptoms and signs of schizophrenia [1-3]. However, evidence suggests that substantial improvements can occur within 2 weeks following the treatment initiation or even as short as 24 hours [4, 5]. Besides, symptom relief during the first 2 weeks is more striking than during the second 2 weeks of treatment [6, 7]. Overall, responses to antipsychotic medications are considered to be immediate. Administering an antipsychotic medication at the optimal dose for at least 2 weeks before switching to another drug has therefore been highly recommended in guidelines by the Schizophrenia Patients Outcomes Research Team (PORT) and World Federation of Societies of Biological Psychiatry (WFSBP). However, Schennach *et al.* argued that it was more appropriate to make predictions after 6 weeks of treatment [8]. The question of how long clinicians should wait before considering an antipsychotic medication ineffective and then changing the treatment remains unresolved. Previous studies have investigated whether the degree of early improvement can reflect later treatment response, but there are still several limitations [9-15]. Some have compared predictive accuracy for subsequent treatment response in the first- and second-generation antipsychotic medications, but with finite medications in a single study [13, 16, 17]. Therefore, it is still an open question whether switching antipsychotics is more effective than administering the same drug in the early phase. Generally, most of the previous studies had been blemished in the following respects: 1) Sample sizes were not large enough in individual studies [7, 13]; 2) Meta-analyses that pooled randomized controlled trial (RCT) studies were handled by different researchers, and the long intervals among them could give rise to phenomenal clinical heterogeneity; 3) So far, there has been no Chinese population-based RCT study incorporating over 3000 schizophrenics in which the first-onset patients were nearly up to 1000, although a much smaller-scale one was once conducted [18].

Thus, we carried out a large-scale RCT to identify the effectiveness of predicting responses to 7 antipsychotic medications in a sample of 3010 Chinese patients with schizophrenia. In this way, we explored whether the early efficacy of antipsychotic drugs can predict the subsequent efficacy. If so, how early would the timing be? And how does the capacity for predicting vary among different antipsychotics and symptoms?

2. METHODS

2.1. Participants

Data were obtained from a multicenter, randomized, open-label clinical trial to compare the treatment effectiveness of 7 antipsychotic drugs in first-onset and relapsed patients with schizophrenia. We recruited 3010 patients with schizophrenia from 32 clinical settings from July 20th, 2017, to Feb 10th, 2018, all enrolled in the Chinese Antipsychotic Pharmacogenomic Consortium (CAPOC). Criteria of inclusion and exclusion are elaborated in APPENDIX (**A**). Consistent diagnoses were made by at least two experienced psychiatrists based on unstructured interviews [19] with patients and families and a review of medical records. Symptom severity was measured through PANSS [20], a 30-item scale for assessing schizophrenic symptoms. All participants received 6 weeks of treatment with one antipsychotic drug randomly chosen from five atypical antipsychotics (risperidone 2-6 mg/d, olanzapine 5-20 mg/d, quetiapine 400-750 mg/d, aripiprazole 10-30 mg/d, and ziprasidone 80-160 mg/d) and two typical antipsychotics (perphenazine 20-60 mg/d, and haloperidol 6-20 mg/d). According to the study protocol, the first 2 weeks of treatment were spent on drug titration and the next 4 weeks were the maintenance period. The upper limit of antipsychotic dosage had to be higher than the median lower doses of the target dosage range, as recommended by the International Consensus Study of Antipsychotic Dosing [21]. Patients were excluded if there were serious adverse effects at any time during the 6 weeks.

2.2. Clinical Evaluations

PANSS data were collected biweekly from baseline to week 6. All raters were trained, and high inter-rater reliability was achieved. Side effects were evaluated through BARS (Barnes Akathisia Scale) [22], AIMS (Abnormal Involuntary Movement Scale) [23] and EPS (Extrapyramidal Symptom Rating Scale) [24] (ANOVA-ICC>0.8). Investigators, medical staff and patients were all blinded to treatment assignment. The administration of other psychotropics was considered a violation of the regulations of concomitant medication, except short-acting benzodiazepines for insomnia and lorazepam for agitation and psychotic anxiety. Additionally, the anticholinergic drug hyoscine (up to 6 mg/d) could be prescribed for extrapyramidal symptoms and beta-blocker propranolol (up to 80 mg/d) for akathisia.

2.3. Statistics

To define the changes in mental health, 30-point subtraction, the lowest possible PANSS total score, was subtracted [25, 26]. A threshold of 50% reduction was set [27, 28], labeling patients with a ≥50% probability of remission "responders" and those with a <50% probability "non-responders". We employed 2 models: 1) a logistic regression model with a cut-off value of 50% reduction verified whether the reduction rate of the overall PANSS scores can be a predictor; 2) a random forest model based on 30 items of PANSS, in which imputed data was incorporated and then randomly assigned to a training set and a test set at a ratio of 3:1, was applied to further check whether improvement of a single symptom can be an identifier. ROC curves of predictions using early treatment improvement were plotted, with both crude and adjusted area under the curve (AUC) estimated [29]. Additionally, through the random forest model, the mean decrease accuracy and mean decrease Gini of each PANSS item came into being, and the two mean values

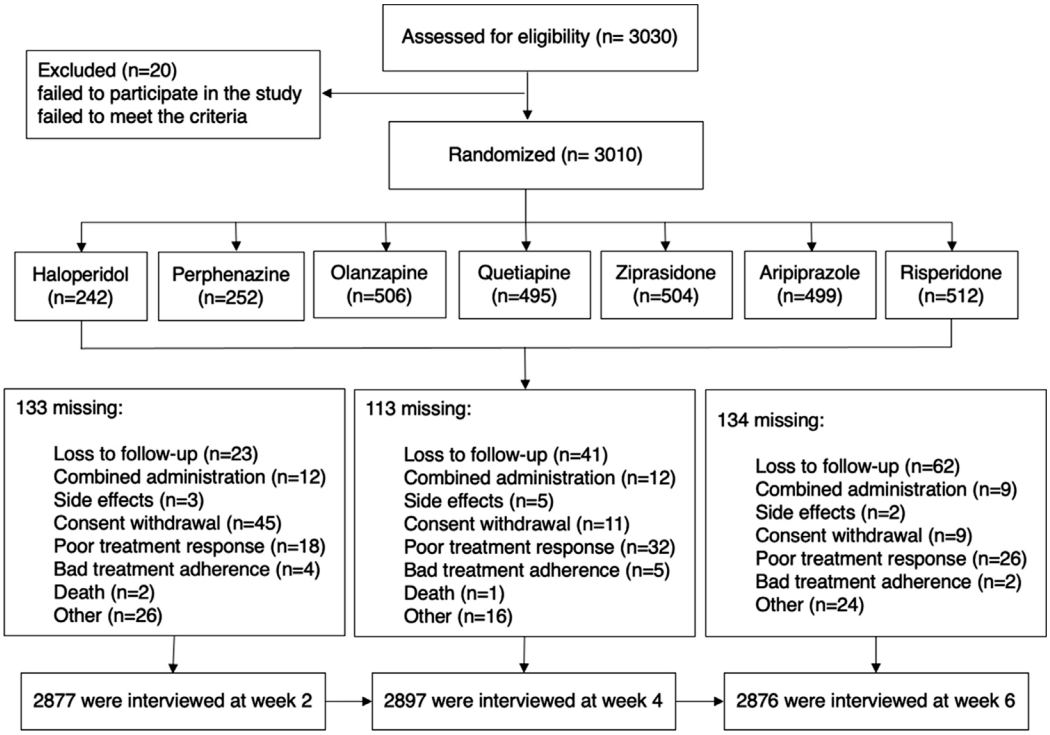

Fig. (1). Trial profile.

helped identify how much the relief of each symptom at week 2 contributed to such predictions. More statistical details concerning predictions for later responses were elucidated in APPENDIX (**B**). All the statistical analyses above were performed in R 3.6.2 and Stata 15.1.

3. RESULTS

3.1. Participant Characteristics

Of 3010 patients, 133 (4.42%), 113 (3.75%) and 134 (4.45%) cases were missed at the time point of the 2nd, 4th, and 6th week, respectively, due to a loss to follow-up, combined administration of other drugs, medication side effects, consent withdrawal, poor treatment response, inadequate treatment adherence, death and other conditions violating inclusion criteria or continuation of treatment (Fig. **1**). Baseline demographics and severity of illness are described in Supplemental Tables **S1** and **S2**. There was no significant difference in data after imputation (p>0.05).

A portfolio of demographics, baseline characteristics and clinical profiles of first-onset and relapsed patients are shown in Table **1**. All participants (N = 3010) were Han Chinese with a mean age of 31.42 years (SD=8.26), among which 51.1% were female. At baseline, the mean total score of PANSS was 89.42 (SD=15.31), and mean scores of positive symptoms, negative symptoms and general psychopathology were 25.51 (SD=4.70), 21.77 (SD=6.75) and 42.14 (SD=8.44), respectively. There were 865 (28.7%) patients suffering from their first onset at the time of initial evaluation, while the remaining 2145 patients had at least one episode before the enrollment of this study. There were no statistically significant disparities in gender, family history, educational attainment or baseline PANSS scores of the overall scale, positive subscale and general psychopathology subscale between the first-onset and relapsed participants. The clinical profiles of patients treated with the seven antipsychotics are exhibited in Supplemental Table **S2**. No significant difference was observed in gender, age, age of onset, first onset, illness course, family history, educational attainment, body mass index or baseline PANSS negative severity.

3.2. Improvement in Clinical Manifestations

During the 6-week evaluation, the average reduction rates of PANSS total score in the overall sample were 25.27%, 43.94% and 52.32% at the end of the 2^{nd}, 4^{th} and 6^{th} week, respectively. According to the response criteria of 50% reduction at week 6, 1682 patients (55.88%) were classified as treatment responders, among whom 497 were afflicted with their first onset of schizophrenia. The comparison between responders and non-responders at week 6 revealed significant differences in age of onset, illness course, educational attainment and severity of both positive and negative symptoms, with the former scoring higher on the PANSS positive subscale but lower on the negative subscale at baseline. Details are shown in Table **1**.

3.3. Predictions of Subsequent Response Using Early Efficacy

As profiled in Fig. (**2**), ROC curves of the PANSS reduction rate at week 2 and week 4 produced by the logistic regression model were generated for all patients, respectively. In the overall sample, the best threshold of the reduction rate

Table 1. Demographics, baseline characteristics and clinical profiles of first-onset and relapsed patients.

-	Overall (N=3010)	First Onset / Relapse (N=865 / 2145)	Cut-Off = 50%			Cut-Off = 25%		
			Responder / Non-Responder (N=1682 / 1328)	First-Onset Responder/ Non-Responder (N=497 / 368)	Relapsed Responder/ Non-Responder (N=1185 / 960)	Responder / Non-Responder (N=2504 / 506)	First-Onset Responder/ Non-Responder (N=712 / 153)	Relapsed Responder/ Non-Responder (N=1792 / 353)
Gender female, n (%)	1538 (51.10)	445/1093 (51.40/51.00)	863/675 (51.30/50.80)	243/202 (48.90/54.90)	620/473 (52.30/49.30)	1289/249 (51.05/49.20)	358/87 (50.30/56.90)	931/162 (52.00/45.90)*
Age, years (mean (SD))	31.42 (8.26)	28.95/32.42 (8.20/8.07)***	31.34/31.53 (8.22/ 8.32)	29.05/28.82 (8.16/8.26)	32.30/32.57 (8.05/8.11)	31.45/31.31 (8.22/8.46)	29.05/28.50 (8.22/8.13)	32.40/32.52 (8.03/8.33)
Age of onset, years (mean (SD))	25.26 (6.96)	26.78/24.65 (7.44/6.66)***	25.69/24.72 (7.13/6.69)***	27.32/26.04 (7.66/7.08)*	25.00/24.21 (6.79/6.47)**	25.42/24.48 (7.04/6.49)**	27.07/25.42 (7.54/6.85)*	24.76/24.07 (6.72/6.30)
First onset, n (%)	865 (28.70)	-	497/368 (29.50/27.70)	-	-	712/153 (28.40/30.20)	-	-
Illness course, years (mean (SD))	6.16 (5.94)	2.17/7.77 (3.48/5.96)***	5.65/6.81 (5.80/6.04)***	1.72/2.78 (2.85/4.12)***	7.29/8.36 (5.93/5.95)***	6.03 /6.83 (5.85/6.30)**	1.98/3.08 (3.11/4.78)	7.63/8.45 (5.91/6.19)*
Family history, n (%)	641 (21.30)	173/468 (20.00/21.80)	352/289 (20.90/21.80)	98/75 (19.70/20.40)	254/214 (21.40/22.30)	535/106 (21.40/20.90)	149/24 (20.90/15.70)	386/82 (21.50/23.20)
Educational attainment	-	-	***	-	**	**	-	***
Doctorate	3 (0.10)	1/2 (0.10/0.10)	2/1 (0.10/0.10)	1/0 (0.20/0.00)	1/1 (0.10/0.10)	2/1 （0.10/0.20）	1/0 (0.10/0.00)	1/1 (0.10/0.30)
Master	13 (0.40)	3/10 (0.30/0.50)	9/4 (0.50/0.30)	2/1 (0.40/0.30)	7/3 (0.60/0.30)	12/1 （0.50/0.20）	3/0 (0.40/0.00)	9/1 (0.50/0.30)
Bachelor	243 (8.10)	72/171 (8.30/8.00)	122/121 (7.30/9.10)	39/33 (7.80/9.00)	83/88 (7.00/9.20)	188/55 (7.50/10.90)	61/11 (8.60/7.20)	127/44 (7.10/12.50)
College	300 (10.00)	100/200 (11.60/9.30)	153/147 (9.10/11.10)	49/51 (9.90/13.90)	104/96 (8.80/10.00)	244/56 (9.70/11.10)	72/28 (10.10/18.30)	172/28 (9.60/7.90)
High school	778 (25.80)	208/570 (24.00/26.60)	402/376 (23.90/28.30)	118/90 (23.70/24.50)	284/286 (24.00/29.80)	632/146 (25.20/28.90)	175/33 (24.60/21.60)	457/113 (25.50/32.00)
Middle school	1154 (38.30)	326/828 (37.70/38.60)	664/490 (39.50/36.90)	186/140 (37.40/38.00)	478/350 (40.30/36.50)	971/183 (38.80/36.20)	264/62 (37.10/40.50)	707/121 (39.50/34.30)
Primary school	486 (16.10)	144/342 (16.60/15.90)	304/182 (18.10/13.70)	92/52 (18.50/14.10)	212/130 (17.90/13.50)	423/63 (16.90/12.50)	125/19 (17.60/12.40)	298/44 (16.60/12.50)
Illiteracy	33 (1.10)	11/22 (1.30/1.00)	26/7 (1.50/0.50)	10/1 (2.00/0.30)	16/6 (1.40/0.60)	32/1 (1.30/0.20)	11/0 (1.50/0.00)	21/1 (1.20/0.30)
BMI (kg/m^2) (mean (SD))	21.88 (6.96)	21.31/22.11 (9.06/5.89)**	21.94/21.82 (5.65/8.33)	21.12/21.57 (4.49/12.88)	22.28/21.91 (6.03/5.69)	21.98/21.41 (7.18/5.73)	21.38/21.02 (9.63/5.71)	22.22/21.58 (5.91/5.74)
PANSS Total† (mean (SD))	89.42 (15.31)	88.58/89.76 (15.53/15.21)	89.36/89.50 (16.02/14.36)	88.75/88.34 (16.45/14.22)	89.61/89.94 (15.83/14.40)	89.46/89.25 (15.38/14.97)	88.74/87.84 (15.49 /15.76)	89.74/89.86 (15.33/14.60)
PANSS Positive† (mean (SD))	25.51 (4.70)	25.52/25.50 (4.67/4.71)	25.84/25.10 (4.89/4.41)***	25.74/25.23 (4.86/4.39)	25.88/25.04 (4.90/4.42)***	25.60/25.08 (4.71/4.64)*	25.58/25.26 (4.60/4.96)	25.60/25.01 (4.75/4.49)*
PANSS Negative† (mean (SD))	21.77 (6.75)	20.98/22.09 (6.94/6.65)***	21.27/22.40 (7.02/6.33)***	20.50/21.62 (7.12/6.64)*	21.59/22.70 (6.96/6.18)***	21.66/22.33 (6.78/6.58)*	20.87/21.48 (6.94/6.92)	21.97/22.69 (6.69/6.40)
PANSS General† (mean (SD))	42.14 (8.44)	42.08/42.17 (8.43/8.44)	42.25/42.00 (8.60/8.23)	42.51/41.48 (8.75/7.96)	42.14/42.20 (8.54/8.33)	42.20 /41.84 (8.41/8.59)	42.29/41.10 (8.27/9.08)	42.17 /42.16 (8.46/8.36)
PANSS % change (week 2) (mean (SD))	25.27 (17.96)	26.41/24.81 (18.67/17.64)*	32.35/16.30 (17.54/14.05)***	33.18/17.27 (18.11/15.21)***	32.00/15.92 (17.29/13.56)***	27.84/12.52 (17.43/14.84)***	29.09/13.93 (18.08/16.15)***	27.35/11.91 (17.14/14.21)***
PANSS % change (week 4) (mean (SD))	43.94 (22.30)	45.60/43.27 (23.51/21.77)**	56.05/28.60 (17.94/17.28)***	57.72/29.22 (18.91/18.69)***	55.35/28.36 (17.47/16.72)***	48.14/23.14 (20.15/20.74)***	49.99/25.19 (21.24/22.80)***	47.41/22.25 (19.65/19.75)***
PANSS % change (week 6) (mean (SD))	52.32 (26.81)	53.43/51.87 (27.95/26.33)	71.86/27.56 (13.28/17.57)***	73.47/26.36 (13.50/17.73)***	71.19/28.02 (13.13/17.49)***	61.17/8.49 (19.23/11.65)***	63.14/8.22 (19.77/10.66)***	60.39/8.60 (18.96/12.07)***

Abbreviations: PANSS, Positive and Negative Syndrome Scale; PANSS Total, PANSS total scores; PANSS Positive, PANSS scores of positive subscale; PANSS Negative, PANSS scores of negative subscale; PANSS General, PANSS scores of the general psychopathological subscale. PANSS % change, a percentage change of PANSS total scores from the baseline, namely, the reduction rate of PANSS total scores, which was calculated as 100% × (baseline score - endpoint score) / (baseline score - 30). Details of the reduction rate of PANSS are shown in Appendix **B**. ***, *p*-value <0.001; **, *p* value≤0.01; *, *p*-value ≤0.05. †, assessments were carried out at baseline.

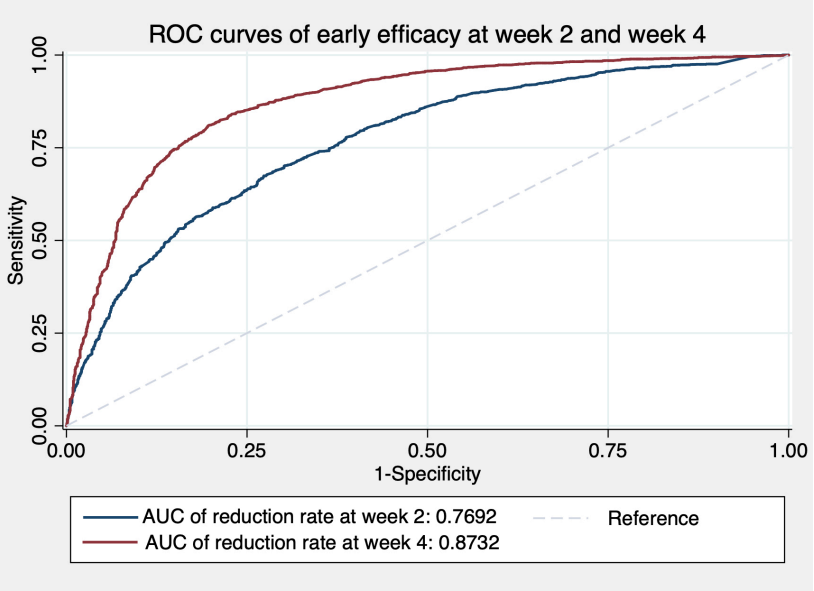

Fig. (2). ROC curves of predictions using the reduction rates of PANSS total scores at week 2 and week 4. With a cut-off of 50% reduction, both reduction rates at week 2 and week 4 enable the subsequent responses to antipsychotics at week 6 to be predicted. **Abbreviation:** AUC, area under the curve.

Table 2. Prediction of responses at week 6 through early efficacy at week 2 and week 4 with cut-off values of 25% and 50%.

(A Cut-Off of 25%/50%)		Threshold	Specificity (%)	Sensitivity (%)	FPR (%)	PPV (%)	NPV (%)	Accuracy (%)	Youden Index (%)	AUC
Overall sample	Week 2 Predicting Week 6[a]	15.48/22.52	69.17/72.67	74.16/67.42	30.83/27.33	92.25/75.75	35.11/63.78	73.32/69.73	1.43/1.40	0.766/0.769
	Week 4 Predicting Week 6[b]	24.56/41.00	64.03/80.35	89.58/80.98	35.97/19.65	92.49/83.92	55.38/76.93	85.28/80.70	1.54/1.61	0.814/0.873
First-onset patients	Week 2 Predicting Week 6[a]	15.43/27.95	66.01/80.71	75.84/57.55	33.99/19.29	91.22/80.11	37.00/58.46	74.10/67.40	1.42/1.38	0.750/0.757
	Week 4 Predicting Week 6[b]	22.59/40.32	56.86/74.73	91.15/83.90	43.14/25.27	90.77/81.76	58.00/77.46	85.09/80.00	1.48/1.59	0.787/0.861
Relapsed patients	Week 2 Predicting Week 6[a]	15.48/22.52	70.54/74.06	73.55/67.17	29.46/25.94	92.69/76.17	34.44/64.64	73.05/70.26	1.44/1.41	0.774/0.774
	Week 4 Predicting Week 6[b]	25.51/40.97	68.27/82.08	88.23/80.34	31.73/17.92	93.38/84.70	53.32/77.18	84.94/81.12	1.56/1.62	0.828/0.878

Abbreviations: FPR, false positive rate; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.
Note: [a]The prediction was achieved by adopting the reduction rate of PANSS total score at week 2 as a predictor. [b] The prediction was achieved by adopting the PANSS total score reduction rate at week 4 as a predictor.

at week 2 was found to be 22.52%, with a specificity of 72.67% and a sensitivity of 67.42%; for the prediction using the reduction rate at week 4, the best threshold of the reduction rate was found to be 41.00%, with a specificity of 80.35% and a sensitivity of 80.98% (Table **2**). ROC curves and confusion matrix produced by the random forest model are shown in Fig. (**3**). The results above derived from the two models jointly indicated that improvement at week 2 and week 4 were both able to predict the efficacy at week 6. Moreover, in the adjusted model in which age, gender, educational attainment, family history, illness course and baseline severities of psychotic symptoms served as covariates (Supplemental Table **S3**), results didn't deviate from the primary outcome that the early efficacy at week 2 and week 4 could both successfully predict subsequent responses to antipsychotics, although the efficacy at week 4 performed comparatively better in such a forecast. When taking baseline PANSS total score as a portfolio of covariates, we found that the phenomenal effect of the baseline illness severity on subsequent efficacy (p=0.000) was largely boiled down to the role of negative symptoms (p=0.000), whereas scores of positive (p=0.148) and general psychopathological (p=0.545) symptoms turned out to be nonsignificant covariates after adjustment.

3.4. Predictive Capacities of 7 Antipsychotics

ROC curves of reduction rates at week 2 were plotted for 7 antipsychotic drugs, respectively (Fig. **4**). Capacities of each antipsychotic for predicting subsequent response using the reduction rate of PANSS items are elucidated in Supplemental Table **S4**. No significant differences were observed

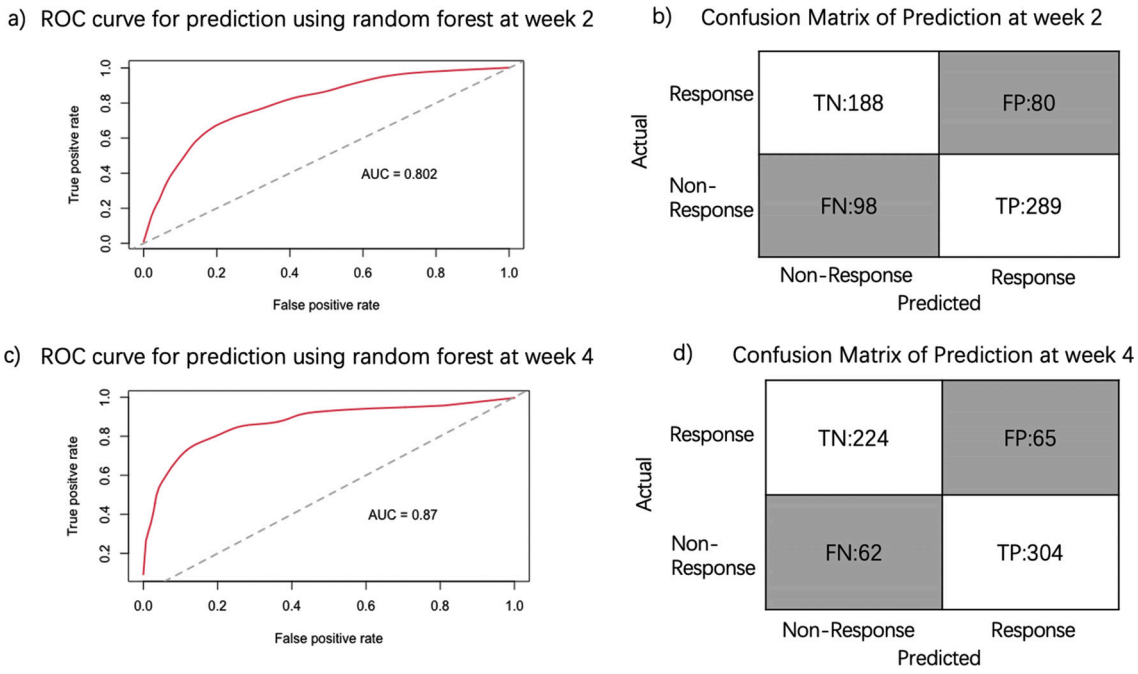

Fig. (3). Predictions of subsequent efficacy using random forest model. With a training set and a test set at a ratio of 3:1, a random forest model based on each PANSS item was employed to verify the predictions. **Abbreviations**: TN, true negative; TP, true positive; FN, false positive; FP, false positive; AUC, area under the curve. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

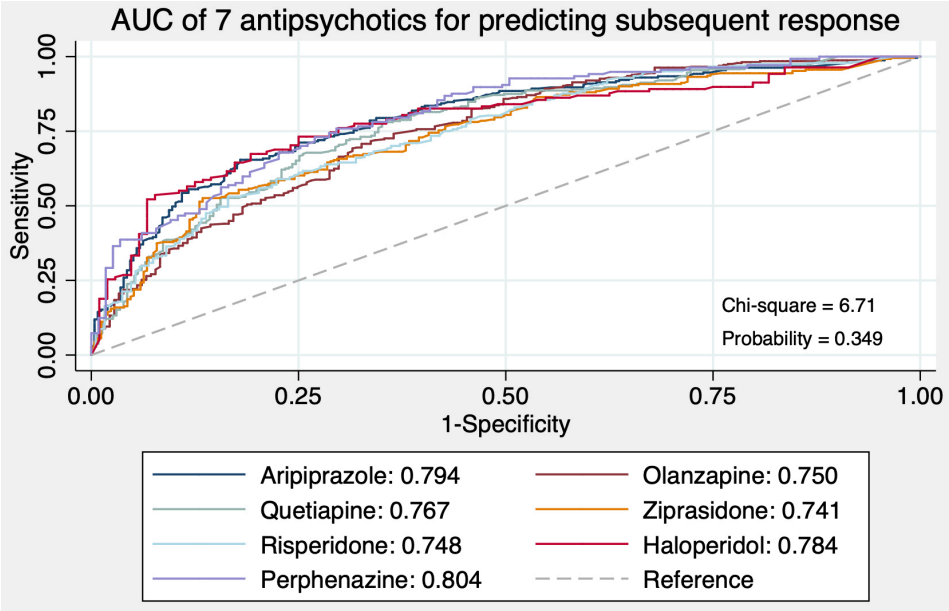

Fig. (4). ROC curves of predictive capacities of 7 antipsychotics at week 2. 7 antipsychotics enjoyed great capacity for predicting subsequent responses with no significant difference. **Abbreviation**: AUC, area under the curve. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

across the AUCs of the 7 agents (chi-square = 6.71, p = 0.349) (Supplemental Table **S5**). However, compared with SGAs, the remission of positive symptoms at week 2 performed significantly better in predicting subsequent responses in FGAs (Supplemental Table **S6**). The specificity of the 7 antipsychotics was all above 70%, with FGAs of 79.39% and SGAs of 73.99%. Moreover, with regard to sensitivity, except for ziprasidone, which had a sensitivity of 53.95%, the remaining fluctuated between 60.98% and 75.00%. Details concerning the efficacy of the 7 antipsychotics as predictors are displayed in Table (**3**).

3.5. Contributions of Psychotic Symptoms to Predictions

Mean decrease accuracy and mean decrease Gini, two important indicators in random forests denoted the relative significance of the variables' role in predictions. For both, the higher the value is, the greater importance will be attached to the symptom. The top ten contributors among the

Table 3. Prediction of responses at week 6 using the overall efficacy of seven different antipsychotics at week 2.

Antipsychotics	Threshold	Specificity (%)	Sensitivity (%)	Accuracy (%)	TN	TP	FN	FP	PPV (%)	NPV (%)	AUC†
FGAs	0.23	79.39%	70.61%	74.30%	131	161	67	34	82.56%	66.16%	0.794
Haloperidol	0.23	78.21%	75.00%	76.32%	61	84	28	17	83.17%	68.54%	0.784
Perphenazine	0.22	80.46%	67.24%	72.91%	70	78	38	17	82.11%	64.81%	0.804
SGAs	0.22	73.99%	68.58%	70.81%	640	847	388	225	79.01%	62.26%	0.764
Aripiprazole	0.27	87.56%	66.07%	76.02%	169	148	76	24	86.05%	68.98%	0.794
Olanzapine	0.21	70.07%	71.02%	70.70%	103	201	82	44	82.04%	55.68%	0.750
Quetiapine	0.22	75.92%	65.93%	70.50%	145	149	77	46	76.41%	65.32%	0.767
Ziprasidone	0.28	89.01%	53.95%	70.44%	170	116	99	21	84.67%	63.20%	0.741
Risperidone	0.26	79.72%	60.98%	67.21%	114	175	112	29	85.78%	50.44%	0.748

Abbreviations: TN, true negative; TP, true positive; FN, false positive; FP, false positive; AUC, area under the curve; FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics.
Note: AUC†: No significant differences were observed in comparing AUCs of the 7 antipsychotics. Detailed comparisons of predicting capacity among seven antipsychotics and between FGAs and SGAs are expounded in Supplemental Table **S5**.

Table 4. Top ten symptom relief contributing to the predictions of subsequent response using random forests.

Week 2 Predicting Week 6			Week 4 Predicting Week 6		
Symptom	Accuracy†	Gini†	Symptom	Accuracy†	Gini†
Delusions	31.76	47.66	Delusions	34.33	64.81
Lack of judgment & insight	28.43	40.76	Lack of judgment & insight	33.63	55.77
Unusual thought content	27.11	41.15	Unusual thought content	33.10	55.78
Suspiciousness/persecution	21.84	37.49	Suspiciousness/persecution	28.82	55.94
Hallucinatory behavior	20.01	36.07	Conceptual disorganisation	27.99	41.95
Conceptual disorganisation	19.97	31.03	Hallucinatory behavior	27.54	47.66
Active social avoidance	19.30	27.46	Hostility	23.90	43.47
Uncooperativeness	19.29	36.04	Lack of spontaneity & flow of conversation	23.12	36.32
Hostility	17.83	33.40	Poor rapport	21.53	35.54
Lack of spontaneity & flow of conversation	16.96	27.81	Uncooperativeness	21.36	36.25

Note: †, mean decrease value; Accuracy†**,** mean decrease accuracy; Gini†, mean decrease Gini. The higher the value, the more critical the corresponding symptom's remission to the prediction of subsequent response.

30 symptoms compiled in the PANSS overall scale are visualized in Table **4**. Among the top ten contributing symptoms, delusions, lack of judgment and insight, unusual thought content, suspiciousness/ persecution, hallucinatory behavior, conceptual disorganisation, uncooperativeness, hostility and lack of spontaneity and flow of conversation carved niches in both predictions using the efficacy at week 2 and 4, the first four being the mainstays for their greatest weight in the random forest model. Additionally, for predictions using efficacy at week 2, active social avoidance also played important roles; for predictions using efficacy at week 4, poor rapport lent support to a certain degree. Contributions of the relief of 30 psychotic symptoms in PANSS to predictions of subsequent responses are elucidated in Supplemental Table **S7**.

4. DISCUSSION

On the basis that the reduction rate at week 2 could successfully predict the efficacy at week 6, we examined the predictive power of different antipsychotics and delved into the contributions of psychotic symptom relief to such predictions. We found that 1) improvement at week 2 was able to clinically predict responses to antipsychotics at week 6, echoing many previous findings that early efficacy can successfully predict subsequent treatment responses [9, 10, 12-14, 16, 30-39]; 2) 7 antipsychotic medications, including two FGAs and five SGAs, demonstrated similar capacities for anticipating the subsequent efficacy, and no significant difference inhered in the type of medications; 3) among all of the symptoms in PANSS, the relief of delusions, lack of judgment and insight, unusual thought content, and suspiciousness/persecution were endowed with the greatest weight in the outcome forecast.

4.1. The Earliest Timing to Predict

In our study, efficacy at week 2 was the earliest time to predict subsequent responses to antipsychotics. Although it

demonstrated comparatively weaker predictive capacity than the improvement at week 4, such timing might exert prodigiously seminal influence upon clinical practice. In this study, early responses to antipsychotics at week 2 could not only predict responses at week 6 but also appeared to be a robust predictor of subsequent non-responses, making adequate provision for switches of the treatment plan. Our results suggested that patients who did not achieve a 22.52% reduction at week 2 were most not likely to reach a 50% response rate at week 6. Therefore, for patients whose improvements at week 2 are not striking enough or remain ineffective, it would be more likely to anticipate little clinical improvement in the ensuing 4 weeks if the same antipsychotic is further administered. At this time, since the prospect of this non-response-prone population's phenomenal improvement remains pretty remote at week 6, clinicians ought to consider remedial measures, such as increasing, switching or adding on. This strategy might be most viable for patients treated with typical antipsychotics because typical antipsychotics may trigger more significant side effects at clinically effective doses than atypical ones [40]. In this study, the early treatment effect of typical antipsychotics groups (AUC of haloperidol and perphenazine = 0.784 and 0.804, respectively; specificity of haloperidol and perphenazine = 78.21% and 80.46%, respectively) could predict the non-response in later period as well. This recommends that if patients treated with typical antipsychotics showed a low response in the early stage, switching medicine in time is urgently needed to avoid invalid treatment and, more importantly, severe side effects.

4.2. Generalizability

With the question of when is the earliest timing to forecast subsequent responses to antipsychotic medications resolved, further exploration of predictive capacities among various antipsychotics is birthed. We found that the AUCs of haloperidol, perphenazine, aripiprazole, olanzapine, quetiapine, ziprasidone and risperidone were all above 0.70. Based on the consensus definition [41], a value of 0.7-0.8 is generally considered an acceptable threshold, and values above 0.8 reflect good discriminative power. Moreover, nonsignificant differences indicated that all these antipsychotics make concerted efforts to forecast long-term efficacy. More importantly, early efficacy can predict subsequent outcomes that might be generalized in antipsychotics.

However, in treating schizophrenia, some patients may have been in remission at the early stage but turned out to be non-responders later due to disease fluctuation, the placebo effect and other reasons. At present, these patients cannot be effectively distinguished, towards which our team managed to divide the early treatment response into a high-trajectory group of better responders and a low-trajectory group of worse responders through unsupervised machine learning K-means for longitudinal data [42]. Since the early relief of psychotic symptoms predict that long-term efficacy could provide a clinically empirical basis to help improve the early identification of poor outcomes, this field is worthy of further investigation [43].

4.3. Cut-off Setting

A lack of consensus over the definition of early improvement and later treatment responses means that guidelines have not been well established yet. Cut-offs in the previous studies were set arbitrarily. Some have defined early improvement and/or later response as a 20% reduction of PANSS total score [9], whereas others used a 30%, 40%, and 50% reduction [44, 45]. Based on previous research, we adopted a 50% reduction rate as the cutoff value in our study, but to draw a broader picture of efficacy prediction, we also provided a 25% reduction as the cut-off value for reference (Table **1**) [18, 28, 46, 47]. Given the response rate at week 6, although a cut-off of 25% improvement may be easier to use in clinical practice and possess higher positive predictive values (PPVs), the 50% reduction rate demonstrated its robustness in multiple arenas, such as specificity analyses and predictive capacity estimations of greater responses [46]. Additionally, several previous studies have supported that this cutoff is clinically meaningful, similar to a CGI rating on how much improved according to the equipper centile linking method [48, 49]. For clinical practice, the high specificity, NPV and AUC are important in guiding the switch to antipsychotics. On the other hand, in the common use of such ROC analyses, it is worth noting that some defects present themselves. One is that the results cannot be generalized due to the small sample size. Therefore, it is essential to evaluate the best suitable cut-off by obtaining sufficient samples. Differences in sample sizes and statistical powers may serve as one of the triggers for different cutoffs adopted in previous studies reporting significant results. In this study, we held a much larger sample size than previous individual studies, and larger PPVs can be obtained if we appropriately sacrifice the power of prediction and decrease AUCs to a certain degree.

4.4. Clinical Application

Although some biological methods have been developed to predict the efficacy of antipsychotics, in practical terms, none of these potential predictors have indeed facilitated the development of a clinically useful decision-making tool to date. However, this study removed the fixed focalization from the PANSS total score and provided fresh insight into the predictive capacities of psychotic symptoms, assisting psychiatric clinicians in evaluating patients' long-term responses to antipsychotics in clinical scenarios. It stands on a vantage point of clinical practice unveiled that not only PANSS scores but also amelioration of psychotic symptoms made concerted efforts in predicting the subsequent responses. Thereby, in clinical practice, if a patient phenomenally improves in delusions, lack of judgment and insight, unusual thought content, suspiciousness/persecution, or any symptom listed in Table **4**, the better his efficacy might be later on if the symptoms mentioned above do not show significant amelioration or even get worse. It is also possible the patient does not respond well to such antipsychotic drugs at the current dosage and, therefore, cannot achieve an ideal level of improvement at week 6. This can urge psychiatric clinicians to change his current treatment plan during the drug titration and turn to alternative strategies by the first two weeks, such as increasing, switching or adding on.

Additionally, although the early improvement of antipsychotic treatment is considered quite a clinically practical tool with a strong capacity for the outcome forecast, a wider range of predictors, such as comorbidity, adverse events,

genome and cognition, functioning, certainly need to be taken into account and be embraced in further research to better achieve long-term predictions and help clinicians make clinical decisions in the future, no matter how challenging it could be.

4.5. Strengths and Limitations

Several strengths and limitations inherent in this study help conjure up a much broader picture of this study. First, the sample was selected according to the criteria of RCT. This may not accurately represent routine clinical practice. Second, similar to other clinical trials, most patients in our study experienced multiple episodes of illness and were exposed to antipsychotic medications before enrollment. The increased course of psychotic symptoms, potential substance abuse and dysfunctional abilities may affect the drug response rates and introduce additional variances in data analysis [50]. Given the large proportion of relapsed patients in this study, the confounding factors brought by this population cannot be underestimated. We did not find significant differences in our main findings between cases with the first onset and multiple episodes. Third, placebo effects could not be strictly controlled. Since benzodiazepines were allowed to be administered as concomitant therapies, some improvements in the initial stage could have been attributed to the effect of benzodiazepines rather than antipsychotic medications. Fourth, it is a well-known problem that the high dropout rate in modern clinical trials of antipsychotics is a difficult issue to solve. However, in this study, on the one hand, after excluding the missing cases at certain time points due to all personal reasons and those offending the eligibility criteria, the sample size of the remaining cases was still very large (2877, 2897 and 2876 were recorded at 2^{nd}, 4^{th} and 6^{th} week, respectively); on the other hand, a series of advanced imputation methods were adopted in trajectory analyses to deal with missing data, such as multiple imputations by the R package MICE. Fifth, previous studies hammered away at longer intervals, which comprised more time points and longer follow-ups. However, for first-onset schizophrenics, the first 6 weeks of treatment are of paramount importance, and such a longitudinal profile creates a sufficiently fertile climate for investigations into the difference in predictions of efficacy between the first-onset and relapsed populations. Additionally, benefits brought by the large sample size, to a certain extent, counteract the effects of shorter periods. Last but not least, since the entry criteria included the lowest threshold of PANSS total score, previous studies found that the baseline severity of symptoms could be somewhat inflated in an attempt to meet these inclusion cut-offs. In this study, a PANSS total score of 60 was set as the lowest limitation. Therefore, the possibility that the baseline severity of symptoms was exaggerated couldn't be fully avoided, which could weaken the validity of prediction using efficacy at week 2. However, after 2 weeks, it corrected the foregoing exaggeration for clinical evaluation.

CONCLUSION

In conclusion, based on an RCT of 3010 people with schizophrenia treated with haloperidol, perphenazine, aripiprazole, olanzapine, quetiapine, ziprasidone and risperidone, this study confirmed that treatment efficacy as responses and non-responses, to antipsychotics at week 6 could be clinically predicted by improvement at week 2, in which 7 antipsychotics enjoyed similar predictive capacities, and the relief of delusions, lack of judgment and insight, unusual thought content, and suspiciousness/ persecution was of importance to such predictions. Overall, this study tremendously highlights the value of early efficacy as a predictor of subsequent responses and advocates that a psychiatric clinician, with the aid of the reduction of PANSS score and the relief of symptoms, should resort to remedial measures in 2 weeks when patients showed poor responses in the early phase.

AUTHORS' CONTRIBUTIONS

Drs T. Li and Q. Wang had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Tang, Wu, and X. Li are joint first authors, and Drs. T. Li and Q. Wang are corresponding authors.

Q. Wang, Yue, Yan, Lu, J. Yang, Q. Tan, H. Zhang, Xin Ma, L. Li, Xiaohong Ma and D. Zhang, T. Li worked on the concept and design.

Q. Wang, X. Li, Hao, Yan, Y. Zhang, L. Tan, Deng, Chen, G. Yang, L. Wang, F. Zhang, K. Li, Lv, Q. Tan, H. Zhang, Xin Ma, F. Yang, C. Wang, Zhao, Ren, Yu, Y. Wang and T. Li acquired, analysed and interpreted the data.

Q. Wang, Tang, Wu, X. Li, Yan, L. Wang and T. Li drafted the manuscript.

Q. Wang, Tang, Wu, X. Li, Yue, Y. Zhang, L. Tan, Deng, Chen, G. Yang, Lu, L. Wang, F. Zhang, J. Yang, K. Li, Lv, Q. Tan, H. Zhang, Xin Ma, F. Yang, L. Li, C. Wang, Xiaohong Ma, Zhao, Ren, Yu, Y. Wang, D. Zhang, and T. Li critically revised the manuscript for important intellectual content.

Q. Wang, Tang, Wu, X. Li, Yue, Y. Zhang, Deng and T. Li conducted the statistical analysis.

Q. Wang, Yue, Deng, F. Yang, D. Zhang, Hu and T. Li raised funds for the manuscript's publication.

Q. Wang, Yue, Yan, Chen, Lu, L. Wang, J. Yang, Lv, H. Zhang, Xin Ma, F. Yang, L. Li, C. Wang, Zhao, Y. Wang, Hu, D. Zhang, G. Zhang, C. Li, Du and T. Li provided administrative, technical and material support.

Q. Wang, J. Yang, H. Zhang, Xin Ma, F. Yang, L. Li, Xiaohong Ma and T. Li supervised.

LIST OF ABBREVIATIONS

AUC	=	Area Under the Curve
CAPOC	=	Chinese Antipsychotic Pharmacogenomic Consortium
PORT	=	Patients Outcomes Research Team
PPVs	=	Positive Predictive Values
RCT	=	Randomized Controlled Trial
WFSBP	=	World Federation of Societies of Biological Psychiatry

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This RCT was registered at the ethical committee of the Sixth Hospital, Peking University for the Chinese Antipsychotics Pharmacogenomics Consortium.

HUMAN AND ANIMAL RIGHTS

No animal were used in this study, Reported experiments on humans were conducted as per Good Clinical Practice guidelines and principles of the Declaration of Helsinki.

CONSENT FOR PUBLICATION

All patients were informed about the aims and methods of the study and asked for their voluntary consent to the publication of their data. All patients provided their consent for the treatment.

AVAILABILITY OF DATA AND MATERIALS

The data are not publicly available because it is information that could violate the privacy of the registered participants.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

APPENDICES

Appendix A

Inclusion and Exclusion Criteria

Inclusion criteria: 1) aged 18 - 45; 2) were Chinese Han population; 3) were diagnosed with schizophrenia using Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) - Patient Version (SCID-P); 4) were physically healthy; 5) laboratory tests were within normal limits.

Exclusion criteria: 1) received a diagnosis of schizoaffective disorder, mental retardation, or other neurocognitive disorders; 2) had a history of serious adverse reactions to the proposed treatments; 3) had a history of treatment resistance, defined by persistent severe symptoms despite an adequate trial of one of the proposed treatments or prior treatment with clozapine; 4) were pregnant or breast-feeding; 5) had a serious and unstable medical condition.

Appendix B

Statistics Concerning Predictions for Later Responses

1. Clinical Evaluation through PANSS

The clinical manifestation evaluation consisted of scores of the overall PANSS scale, positive subscale, negative subscale and general psychopathological subscale. The PANSS total score was adopted as the evaluation index, given that a single subscale was more susceptible to random error than the overall scale. The percent change in the PANSS score from baseline was calculated using the formula below, in which the lowest possible PANSS total score was subtracted to define the clinical amelioration of mental health.

$$\text{PANSS reduction rate} = \left(\frac{\text{PANSS}_{\text{baseline score}} - \text{PANSS}_{\text{endpoint score}}}{\text{PANSS}_{\text{baseline score}} - 30}\right) \times 100\%$$

Reduction rates higher than Q3+1.5×IQR (the third quartile, Q3; interquartile range, IQR) or lower than Q1-1.5×IQR (the first quartile, Q1) were considered outliers. Values replaced these values at the 0.01 and 0.99 quantiles. Multiple imputations achieved by the R package MICE were applied to interpolate missing data. Details are shown in Supplemental Figs. **S1** and **S2**.

2. Prediction for a Later Response Using Early Treatment Improvement

To delve into whether the clinical improvement at weeks 2 and 4 was endowed with a capacity for predicting the subsequent treatment responses at week 6, not only logistic regression adopting a cut-off value of 50% overall reduction but also a random forest model based on each item in PANSS was employed. With the aid of longitudinal trajectories of treatment responses to different antipsychotics, we compared the predictive capacities of different agents at the earliest predicting timing, in which reduced rates of PANSS total score served as the predictor.

ROC curves with AUC values represent the probability of a classifier ranking a randomly chosen positive instance higher than a randomly chosen negative one. Sensitivity, specificity, true positive rate (TPR), false positive rate (FPR), precision, recall, accuracy and error rate were also used to measure the classifying effectiveness. In addition, to diminish the influence exerted by confounding factors, such as age, gender, educational attainment, family history, illness course and severity of schizophrenic symptoms at baseline, which was assessed by positive, negative and general psychopathology subscales, covariates were accommodated in ROC analyses, crude and adjusted estimates given birth to their forms.

3. Prediction for a Later Response Using Psychotic Symptom Relief

Since early improvement at week 2 could successfully predict treatment responses to antipsychotic medications at

week 6, the predictive capacity of psychotic symptoms was also subsumed into our scope, further supporting our findings in a more tangible way. To assess the predictive capacity of each PANSS item, we made better use of the random forest model.

Random forest is a classification method with multiple decision trees at its core. Compared with the models and analysis methods mentioned above, the random forest is endowed with a greater ability to obtain an unbiased estimation generated internally of the generalization error in the process of forest construction and is not prone to overfitting. Additionally, despite serving as a decision tree classifier, random forests also function as a detection, giving estimates of variable importance in the classification. Accuracy and Gini, the impurity of variables, are indexes that help identify how much each variable contributes to the dependent variable with the aid of the corresponding mean decreases. Mean decrease accuracy and mean decrease Gini, respectively, referring to the degree of reduction in accuracy and heterogeneity of observations at each node of classification trees after removing the variable, play critical roles in random forests. The higher the two values are, the more important the symptoms are to predictions of the ensuing clinical responses. By calculating the mean decrease accuracy and mean decrease Gini of each item in the PANSS, how much the early relief of each symptom contributed to the prediction of subsequent responses came into being, in which the predictive power was not affected by multicollinearity, though the explanatory power of the data was affected. The importance of specific multicollinearity features will cancel each other out, thus affecting our understanding and interpretation of features. However, this did not affect the significance of our results that the remission degree of delusions, lack of judgment and insight, unusual thought content and suspiciousness/persecution possess the strongest weight in predicting the subsequent efficacy at week 6.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

REFERENCES

[1] Creese, I.; Burt, D.R.; Snyder, S.H. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science,* **1976**, *192*(4238), 481-483. http://dx.doi.org/10.1126/science.3854 PMID: 3854

[2] Seeman, P.; Lee, T.; Chau-Wong, M.; Wong, K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature,* **1976**, *261*(5562), 717-719. http://dx.doi.org/10.1038/261717a0 PMID: 945467

[3] Kapur, S.; Remington, G. Dopamine D2 receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol. Psychiatry,* **2001**, *50*(11), 873-883. http://dx.doi.org/10.1016/S0006-3223(01)01251-3 PMID: 11743942

[4] Kapur, S.; Arenovich, T.; Agid, O.; Zipursky, R.; Lindborg, S.; Jones, B. Evidence for onset of antipsychotic effects within the first 24 hours of treatment. *Am. J. Psychiatry,* **2005**, *162*(5), 939-946. http://dx.doi.org/10.1176/appi.ajp.162.5.939 PMID: 15863796

[5] Giegling, I.; Porcelli, S.; Balzarro, B.; Andrisano, C.; Schäfer, M.; Möller, H.J.; Rujescu, D.; Serretti, A. Antipsychotic response in the first week predicts later efficacy. *Neuropsychobiology,* **2012**, *66*(2), 100-105. http://dx.doi.org/10.1159/000337739 PMID: 22814310

[6] Agid, O.; Kapur, S.; Arenovich, T.; Zipursky, R.B. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. *Arch. Gen. Psychiatry,* **2003**, *60*(12), 1228-1235. http://dx.doi.org/10.1001/archpsyc.60.12.1228 PMID: 14662555

[7] Leucht, S.; Busch, R.; Hamann, J.; Kissling, W.; Kane, J.M. Early-onset hypothesis of antipsychotic drug action: a hypothesis tested, confirmed and extended. *Biol. Psychiatry,* **2005**, *57*(12), 1543-1549. http://dx.doi.org/10.1016/j.biopsych.2005.02.023 PMID: 15953491

[8] Schennach, R.; Riesbeck, M.; Mayr, A.; Seemüller, F.; Maier, W.; Klingberg, S.; Heuser, I.; Klosterkötter, J.; Gastpar, M.; Schmitt, A.; Sauer, H.; Schneider, F.; Jäger, M.; Wölwer, W.; Gaebel, W.; Möller, H.J.; Riedel, M. Should early improvement be re-defined to better predict the maintenance of response in first-episode schizophrenia patients? *Acta Psychiatr. Scand.,* **2013**, *127*(6), 474-481. http://dx.doi.org/10.1111/acps.12006 PMID: 22957829

[9] Samara, M.T.; Leucht, C.; Leeflang, M.M.; Anghelescu, I.G.; Chung, Y.C.; Crespo-Facorro, B.; Elkis, H.; Hatta, K.; Giegling, I.; Kane, J.M.; Kayo, M.; Lambert, M.; Lin, C.H.; Möller, H.J.; Pelayo-Terán, J.M.; Riedel, M.; Rujescu, D.; Schimmelmann, B.G.; Serretti, A.; Correll, C.U.; Leucht, S. Early improvement as a predictor of later response to antipsychotics in schizophrenia: a diagnostic test review. *Am. J. Psychiatry,* **2015**, *172*(7), 617-629. http://dx.doi.org/10.1176/appi.ajp.2015.14101329 PMID: 26046338

[10] Kinon, B.; Chen, L.; Aschersvanum, H.; Stauffer, V.; Kollackwalker, S.; Sniadecki, J.; Kane, J. Predicting response to atypical antipsychotics based on early response in the treatment of schizophrenia. *Schizophr. Res.,* **2008**, *102*(1-3), 230-240. http://dx.doi.org/10.1016/j.schres.2008.02.021 PMID: 18423985

[11] Lin, C.H.; Chou, L.S.; Lin, C.H.; Hsu, C.Y.; Chen, Y.S.; Lane, H.Y. Early prediction of clinical response in schizophrenia patients receiving the atypical antipsychotic zotepine. *J. Clin. Psychiatry,* **2007**, *68*(10), 1522-1527. http://dx.doi.org/10.4088/JCP.v68n1008 PMID: 17960966

[12] Stauffer, V.L.; Case, M.; Kinon, B.J.; Conley, R.; Ascher-Svanum, H.; Kollack-Walker, S. Early response to antipsychotic therapy as a clinical marker of subsequent response in the treatment of patients with first-episode psychosis. *Psychiatry Res,* **2010**, *187*, 42-8. http://dx.doi.org/10.1016/j.psychres.2010.11.017

[13] Schennach-Wolff, R.; Seemüller, F.H.; Mayr, A.; Maier, W.; Klingberg, S.; Heuser, I.; Klosterkötter, J.; Gastpar, M.; Häfner, H.; Sauer, H.; Schneider, F.; Gaebel, W.; Jäger, M.; Möller, H.J.; Riedel, M. An early improvement threshold to predict response and remission in first-episode schizophrenia. *Br. J. Psychiatry,* **2010**, *196*(6), 460-466. http://dx.doi.org/10.1192/bjp.bp.109.069328 PMID: 20513856

[14] Leucht, S.; Zhao, J. Early improvement as a predictor of treatment response and remission in patients with schizophrenia: A pooled, post-hoc analysis from the asenapine development program. *J. Psychopharmacol.,* **2014**, *28*(4), 387-394. http://dx.doi.org/10.1177/0269881113517956 PMID: 24429222

[15] Leucht, S.; Shamsi, S.A.R.; Busch, R.; Kissling, W.; Kane, J.M. Predicting antipsychotic drug response – Replication and extension to six weeks in an international olanzapine study. *Schizophr. Res.,* **2008**, *101*(1-3), 312-319. http://dx.doi.org/10.1016/j.schres.2008.01.018 PMID: 18308513

[16] Schennach-Wolff, R.; Jäger, M.; Mayr, A.; Meyer, S.; Kühn, K.U.; Klingberg, S.; Heuser, I.; Klosterkötter, J.; Gastpar, M.; Schmitt, A.; Schlösser, R.; Schneider, F.; Gaebel, W.; Seemüller, F.; Möller, H.J.; Riedel, M. Predictors of response and remission in the acute treatment of first-episode schizophrenia patients — Is it all about early response? *Eur. Neuropsychopharmacol.,* **2011**, *21*(5), 370-378. http://dx.doi.org/10.1016/j.euroneuro.2010.10.003 PMID: 21255982

[17] Schooler, N.; Rabinowitz, J.; Davidson, M.; Emsley, R.; Harvey, P.D.; Kopala, L.; McGorry, P.D.; Van Hove, I.; Eerdekens, M.; Swyzen, W.; De Smedt, G. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am. J. Psychiatry,* **2005**, *162*(5), 947-953. http://dx.doi.org/10.1176/appi.ajp.162.5.947 PMID: 15863797

[18] Chen, Y.L.; Chen, K.P.; Chiu, C.C.; Tai, M.H.; Lung, F.W. Early predictors of poor treatment response in patients with schizophrenia treated with atypical antipsychotics. *BMC Psychiatry,* **2018**, *18*(1), 376. http://dx.doi.org/10.1186/s12888-018-1950-1 PMID: 30509308

[19] First, M.; Spitzer, R.; Gibbon, M. *Structured Clinical Interview for DSM-IV Axis I Disorders--Administration Booklet*; American Psychiatric Press: Washington D.C., **1994**.

[20] Kay, S.R.; Fiszbein, A.; Opler, L.A. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.,* **1987**, *13*(2), 261-276. http://dx.doi.org/10.1093/schbul/13.2.261 PMID: 3616518

[21] Gardner, D.M.; Murphy, A.L.; O'Donnell, H.; Centorrino, F.; Baldessarini, R.J. International consensus study of antipsychotic dosing. *Am. J. Psychiatry,* **2010**, *167*(6), 686-693. http://dx.doi.org/10.1176/appi.ajp.2009.09060802 PMID: 20360319

[22] Barnes, T.R.E. A rating scale for drug-induced akathisia. *Br. J. Psychiatry,* **1989**, *154*(5), 672-676. http://dx.doi.org/10.1192/bjp.154.5.672 PMID: 2574607

[23] Guy, E. Rockville National Institute of Mental Health, U.S. Department of Health and Human Services, M.D. *Abnormal Involuntary Movement Scale. Rockville,. ECDEU Assessment Manual for Psychopharmacology: revised 1976*; National Institute of Mental Health, U.S. Department of Health and Human Services: Rockville, MD, **1976**.

[24] Simpson, G.M.; B, M.; B, G.H.; Angus, J.W.S.; P, F.R.C.; M, D.P. A rating scale for extrapyramidal side effects. *Acta Psychiatr. Scand.,* **1970**, *45*(S212), 11-19. http://dx.doi.org/10.1111/j.1600-0447.1970.tb02066.x PMID: 4917967

[25] Obermeier, M.; Mayr, A.; Schennach-Wolff, R.; Seemüller, F.; Möller, H.J.; Riedel, M. Should the PANSS be rescaled? *Schizophr. Bull.,* **2010**, *36*(3), 455-460. http://dx.doi.org/10.1093/schbul/sbp124 PMID: 19889950

[26] Leucht, S.; Kissling, W.; Davis, J.M. The PANSS should be rescaled. *Schizophr. Bull.,* **2010**, *36*(3), 461-462. http://dx.doi.org/10.1093/schbul/sbq016 PMID: 20357133

[27] Carbon, M.; Correll, C.U. Clinical predictors of therapeutic response to antipsychotics in schizophrenia. *Dialogues Clin. Neurosci.,* **2014**, *16*(4), 505-524. http://dx.doi.org/10.31887/DCNS.2014.16.4/mcarbon PMID: 25733955

[28] Leucht, S.; Kane, J.; Kissling, W.; Hamann, J.; Etschel, E.; Engel, R. What does the PANSS mean? *Schizophr. Res.,* **2005**, *79*(2-3), 231-238. http://dx.doi.org/10.1016/j.schres.2005.04.008 PMID: 15982856

[29] Mossman, D.; Somoza, E. ROC curves, test accuracy, and the description of diagnostic tests. *J. Neuropsychiatry Clin. Neurosci.,* **1991**, *3*(3), 330-333. http://dx.doi.org/10.1176/jnp.3.3.330 PMID: 1821250

[30] Chang, Y.C.; Lane, H.Y.; Yang, K.H.; Huang, C.L. Optimizing early prediction for antipsychotic response in schizophrenia. *J. Clin. Psychopharmacol.,* **2006**, *26*(6), 554-559. http://dx.doi.org/10.1097/01.jcp.0000246211.95905.8c PMID: 17110810

[31] Lieberman, J.A. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia: efficacy, safety and cost outcomes of CATIE and other trials. *J. Clin. Psychiatry,* **2007**, *68*(2), e04. http://dx.doi.org/10.4088/JCP.0207e04 PMID: 17335312

[32] Levine, S.Z.; Leucht, S. Early symptom response to antipsychotic medication as a marker of subsequent symptom change: An eighteen-month follow-up study of recent episode schizophrenia. *Schizophr. Res.,* **2012**, *141*(2-3), 168-172. http://dx.doi.org/10.1016/j.schres.2012.08.030 PMID: 22995933

[33] Chen, L.; Ascher-Svanum, H.; Stauffer, V.; Kinon, B.J.; Kollack-Walker, S.; Ruberg, S. Optimal thresholds of early response to atypical antipsychotics: Application of signal detection methods. *Schizophr. Res.,* **2009**, *113*(1), 34-40. http://dx.doi.org/10.1016/j.schres.2009.06.001 PMID: 19564097

[34] Lambert, M.; Schimmelmann, B.G.; Naber, D.; Eich, F.X.; Schulz, H.; Huber, C.G.; Karow, A. Early- and delayed antipsychotic response and prediction of outcome in 528 severely impaired patients with schizophrenia treated with amisulpride. *Pharmacopsychiatry,* **2009**, *42*(6), 277-283. http://dx.doi.org/10.1055/s-0029-1234105 PMID: 19924588

[35] Chou, Y.H.; Chiu, N.M.; Yang, T.T.; Feng, J.; Chan, C.C.; Lee, H.K. An early improvement in depressive symptoms predicts symptomatic remission of schizophrenia treated with quetiapine. *Int. Clin. Psychopharmacol.,* **2013**, *28*(5), 255-260. http://dx.doi.org/10.1097/YIC.0b013e328363aa33 PMID: 23820333

[36] Yeh, E.-C.; Huang, M.-C.; Tsai, C.-J.; Chen, C.-T.; Chen, K.-Y.; Chiu, C.-C. Early treatment response predicted subsequent clinical response in patients with schizophrenia taking paliperidone extended-release. *Psychiatry Res.,* **2015**, *230*(1), 13-18. http://dx.doi.org/10.1016/j.psychres.2015.07.037 PMID: 26319696

[37] Leucht, S.; Busch, R.; Kissling, W.; Kane, J.M. Early prediction of antipsychotic nonresponse among patients with schizophrenia. *J. Clin. Psychiatry,* **2007**, *68*(3), 352-360. http://dx.doi.org/10.4088/JCP.v68n0301 PMID: 17388703

[38] Emsley, R.; Rabinowitz, J.; Medori, R. Time course for antipsychotic treatment response in first-episode schizophrenia. *Am. J. Psychiatry,* **2006**, *163*(4), 743-745. http://dx.doi.org/10.1176/ajp.2006.163.4.743 PMID: 16585455

[39] Derks, E.M.; Fleischhacker, W.W.; Boter, H.; Peuskens, J.; Kahn, R.S.; Group, E.S. Antipsychotic drug treatment in first-episode psychosis: should patients be switched to a different antipsychotic drug after 2, 4, or 6 weeks of nonresponse? *J. Clin. Psychopharmacol.,* **2010**, *30*(2), 176-180. http://dx.doi.org/10.1097/JCP.0b013e3181d2193c PMID: 20520291

[40] Meltzer, H.Y. Update on typical and atypical antipsychotic drugs. *Annu. Rev. Med.,* **2013**, *64*(1), 393-406. http://dx.doi.org/10.1146/annurev-med-050911-161504 PMID: 23020880

[41] Weinstein, MC *Clinical Decision Analysis*; WB Saunders: Philadelphia, **1980**.

[42] Dai, M.; Wu, Y.; Tang, Y.; Yue, W.; Yan, H.; Zhang, Y.; Tan, L.; Deng, W.; Chen, Q.; Yang, G.; Lu, T.; Wang, L.; Yang, F.; Zhang, F.; Yang, J.; Li, K.; Lv, L.; Tan, Q.; Zhang, H.; Ma, X.; Li, L.; Wang, C.; Ma, X.; Zhang, D.; Yu, H.; Zhao, L.; Ren, H.; Wang, Y.; Hu, X.; Zhang, G.; Du, X.; Wang, Q.; Li, T. Longitudinal trajectory analysis of antipsychotic response in patients with schizophrenia: 6-week, randomised, open-label, multicentre clinical trial. *BJPsych Open,* **2020**, *6*(6), e126. http://dx.doi.org/10.1192/bjo.2020.105 PMID: 33090091

[43] Ortiz, B.B.; Higuchi, C.H.; Noto, C.; Joyce, D.W.; Correll, C.U.; Bressan, R.A.; Gadelha, A. A symptom combination predicting treatment-resistant schizophrenia – A strategy for real-world clinical practice. *Schizophr. Res.,* **2020**, *218*, 195-200. http://dx.doi.org/10.1016/j.schres.2020.01.002 PMID: 31956005

[44] Kinon, B.J.; Chen, L.; Ascher-Svanum, H.; Stauffer, V.L.; Kollack-Walker, S.; Zhou, W.; Kapur, S.; Kane, J.M. Early response to antipsychotic drug therapy as a clinical marker of subsequent response in the treatment of schizophrenia. *Neuropsychopharmacology,* **2010**, *35*(2), 581-590. http://dx.doi.org/10.1038/npp.2009.164 PMID: 19890258

[45] Stentebjerg-Olesen, M.; Ganocy, S.J.; Findling, R.L.; Chang, K.; DelBello, M.P.; Kane, J.M.; Tohen, M.; Jeppesen, P.; Correll, C.U. Early response or nonresponse at week 2 and week 3 predict ultimate response or nonresponse in adolescents with schizophrenia treated with olanzapine: results from a 6-week randomized, placebo-controlled trial. *Eur. Child Adolesc. Psychiatry,* **2015**, *24*(12), 1485-1496. http://dx.doi.org/10.1007/s00787-015-0725-1 PMID: 26032132

[46] Leucht, S.; Davis, J.M.; Engel, R.R.; Kane, J.M.; Wagenpfeil, S. Defining 'response' in antipsychotic drug trials: recommendations for the use of scale-derived cutoffs. *Neuropsychopharmacology,* **2007**, *32*(9), 1903-1910. http://dx.doi.org/10.1038/sj.npp.1301325 PMID: 17287825

[47] Leucht, S. Measurements of response, remission, and recovery in schizophrenia and examples for their clinical application. *J. Clin. Psychiatry,* **2014**, *75*(Suppl. 1), 8-14. http://dx.doi.org/10.4088/JCP.13049su1c.02 PMID: 24581453

[48] Leucht, S.; Rothe, P.; Davis, J.M.; Engel, R.R. Equipercentile linking of the BPRS and the PANSS. *Eur. Neuropsychopharmacol.,* **2013**, *23*(8), 956-959. http://dx.doi.org/10.1016/j.euroneuro.2012.11.004 PMID: 23433639

[49] Leucht, S.; Engel, R.R.; Davis, J.M.; Kissling, W.; Meyer zur Capellen, K.; Schmauß, M.; Messer, T. Equipercentile linking of the Brief Psychiatric Rating Scale and the Clinical Global Impression Scale in a catchment area. *Eur. Neuropsychopharmacol.,* **2012**, *22*(7), 501-505. http://dx.doi.org/10.1016/j.euroneuro.2011.11.007 PMID: 22386773

[50] Zhang, J.P.; Malhotra, A.K. Pharmacogenetics of antipsychotics: recent progress and methodological issues. *Expert Opin Drug Metab Toxicol,* **2012**, *9*, 183-91. http://dx.doi.org/10.1517/17425255.2013.736964