Early Prediction of Antipsychotic Nonresponse Among Patients With Schizophrenia

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Supported by the American Psychiatric Association/AstraZeneca Young Minds in Psychiatry Award 2004. The study received no other funding.

Presented at the 13th Biennial Schizophrenia Winter Workshop, Feb. 4–10, 2006, Davos, Switzerland.

The authors wish to thank SanofiAventis for allowing use of their original patient data.

Financial disclosure appears at the end of the article.

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Objective: Schizophrenia guidelines recommend waiting several weeks before major changes in antipsychotic treatment are implemented. If, however, nonresponders could be identified shortly after treatment initiation, considerable time could be saved by rapidly switching such patients to potentially more effective alternatives. We therefore attempted to identify what degree of nonresponse shortly after initiation of antipsychotic drug treatment predicts nonresponse at 4 weeks.

Method: Individual patient data from 7 randomized, controlled antipsychotic drug trials including 1708 patients with schizophrenia or schizophreniform disorder according to DSM-III-R or DSM-IV criteria and positive symptoms (mean ± SD age of 36.0 ± 10.9 years; 1054 men and 654 women) were pooled. Receiver-operator curves and logistic regression analyses were used to predict nonresponse at week 4 from the percentage Brief Psychiatric Rating Scale (BPRS) score change at weeks 1 and 2. Three criteria for nonresponse at week 4 were examined: less than 25% BPRS score reduction, less than 50% BPRS score reduction, and "no remission."

Results: Cutoffs predicting nonresponse at 4 weeks with 90% specificity were virtually no response at week 1 (less than 3%–7% BPRS score reduction) and less than 15%, 25%, and 20% at week 2 for the 3 nonresponse criteria described above, respectively. However, to predict less than 25% BPRS score reduction with a positive predictive value of 80%, the cutoff needed was 0% BPRS score reduction at week 2. When the cutoffs identified were entered in logistic regression analyses together with other parameters, they remained the strongest predictors of nonresponse.

Conclusions: Patients with no improvement of symptoms during the first 2 weeks of treatment are unlikely to respond at week 4 and may benefit from a change of treatment.

(J Clin Psychiatry 2007;68:352–360)

The time course of the antipsychotic drug response is poorly understood. While many textbooks have stated that there is a delay of several weeks in the onset of antipsychotic drug action, recent meta-analyses suggest that the onset is rapid[1,2] and can be separated from that of placebo as early as the first 24 hours.[3] However, these studies were not designed to guide treatment decisions, because they were based on mean changes of symptoms over time rather than on analysis of responder rates. An important clinical question in this area is whether responders and nonresponders can be identified shortly after treatment initiation. Such a prediction could save considerable time, because patients who are likely not to respond to a given drug could then be rapidly switched to a potentially more effective alternative. A number of previous studies have found that a good initial response is associated with a robust later response (e.g., after 4 or 6 weeks of treatment[4–7]). However, these studies were usually small and only of correlative nature; thus, they did not provide clinically usable indicators of future nonresponse. A recent preliminary study used a more clinically meaningful approach by analyzing which degree of response at 1 week predicts nonresponse at 4 weeks.[8] However, the sample was again relatively small, it did not use the appropriate method of receiver-operator curves, it was derived from only 1 center, and a response criterion of questionable clinical relevance was used (at least a 20% reduction of the Brief Psychiatric Rating Scale[9] [BPRS] score from baseline). We therefore conducted a sensitivity-specificity analysis in a large dataset

TAKE-HOME POINTS

- Patients with schizophrenia who have shown *no* reduction in symptoms after a 2-week trial with an antipsychotic drug are unlikely to be minimally improved at week 4 and may therefore benefit from a change of treatment.
- Randomized studies are needed to prove that switching antipsychotics after 2 weeks is really effective.

of double-blind, randomized, multicenter trials to identify clinically usable early predictors for later nonresponse.

METHOD

The Database

We pooled 7 randomized controlled amisulpride studies involving acutely ill patients with schizophrenia.[10–16] These 7 studies represent the manufacturer's complete dataset of acutely ill patients with the exception of 1 study that was not yet available when the project began.[17] A number of earlier and smaller studies comparing amisulpride with conventional antipsychotics have been published, but original patient data are no longer available because of changes in drug ownership.[18–22] Furthermore, we excluded studies on patients with predominantly negative symptoms because the time course of the antipsychotic drug effect may be very different in such patients.[23–25] Descriptions of the latter studies can be found in Leucht et al.[26] Important characteristics of the studies included are presented in Table 1.

All studies were randomized, and all but 1[10] were double-blind. All trials examined patients with schizophrenia or schizophreniform disorder according to DSM-III-R or DSM-IV[27] criteria, and with 1 exception,[11] all required various minimum scores as an inclusion criterion to assure that the patients had positive symptoms. In the only study without scale-defined inclusion thresholds,[11] the mean BPRS score at baseline was 65 and all participants were inpatients, so that highly symptomatic patients were also involved in this study. Only patients with a BPRS psychotic score of at least 12 and at least 2 BPRS psychotic items (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content) rated as moderate or higher and a Clinical Global Impressions (CGI)-Severity of Illness scale score of moderate or higher were included, and 1 potentially ineffective 100-mg/day amisulpride dose group (N = 61) from 1 study[13] was excluded a priori. As described in Table 1, 4 studies used a fixed-dose design.[12–15] Three studies had a flexible-dose design.[10,11,16] However, in Carrière et al.,[11] the doses on the first day were predefined to be 800 mg of amisulpride and 20 mg of haloperidol, and in Sèchter et al.,[16] the amisulpride and risperidone doses were, respectively, 600 mg/day and 6 mg/day (increased during 3 days) in the first week to make sure that effective doses were given early on in treatment.

The 1708 patients received amisulpride (N = 1042), haloperidol (N = 367), flupenthixol (N = 47), or risperidone (N = 252). The mean ± SD BPRS score at baseline was 58.6 ± 14.5, the mean age was 36.0 ± 10.9 years, and the mean weight was 70.6 ± 14.5 kg. There were 1054 men and 654 women; 1674 had schizophrenia (897 paranoid type, 432 disorganized type, 335 undifferentiated type, 10 residual type), and 31 had schizophreniform disorder (the exact diagnosis of 3 patients was not indicated).

Response Criteria

We independently analyzed 3 different criteria for defining response at 4 weeks as follows: (1) 25% or greater reduction of the BPRS score from baseline, (2) at least 50% reduction of the BPRS score from baseline, and (3) the remission criteria by Andreasen et al.,[28] which were primarily based on the BPRS and supplemented by items of the Positive and Negative Syndrome Scale[29] (PANSS) or the Scale for the Assessment of Negative Symptoms.[30] This procedure was necessary because most studies used only the positive and the negative subscale of the PANSS in addition to the BPRS but not the general psychopathology subscale, which contributes 2 items to Andreasen's remission criteria. Obviously, only the symptom criteria, not the time criteria (6 months), were applied.

The choice of these criteria was based on the following rationale. In a recent analysis,[31] we found that a 25% and a 50% reduction of the BPRS total score roughly corresponded to "minimally improved" and "much improved," respectively, according to the clinical impression of the rater as assessed by the CGI, and these results were recently replicated in a large independent sample.[32] We thus considered that all 3 criteria were clinically meaningful in our context. While a criterion reflecting only minimal improvement (25% BPRS score reduction) may not be a good indicator of response in contrast to the 50% cutoff, it may be a good measure of nonresponse. In other words, if a patient is not minimally better at 4 weeks, it is likely that many clinicians would consider a change of therapy. Assume, however, that a patient just missed the 50% criterion, i.e., he had a 49% reduction of the BPRS baseline score, would treatment then be switched? The remission criterion was added because it is a more stringent criterion

Table 1. Characteristics of the Included Studies

Study	Antipsychotic Drug and Daily Dose (mg)	N	Duration (wk)	Selected Inclusion Criteria
Möller et al (1997)[12]	Amisulpride 800	95	6	Inpatients with paranoid, disorganized, or undifferentiated schizophrenia and a minimum of positive symptoms
	Haloperidol 20	96		
Wetzel et al (1998)[15]	Amisulpride 1000/600[a]	70	6	Acutely admitted inpatients with paranoid or undifferentiated schizophrenia and with predominant positive symptoms
	Flupenthixol 25/15[a]	62		
Puech et al (1998)[13]	Amisulpride (100,[b] 400, 800, 1200)	(61, 64, 65, 65)	4	Inpatients with acute exacerbations of paranoid, disorganized, or undifferentiated schizophrenia and with positive symptoms
	Haloperidol 16	64		
Colonna et al (2000)[10]	Amisulpride 200–800	370	51	Inpatients or outpatients with acute exacerbations of paranoid, disorganized, or undifferentiated schizophrenia and a minimum of positive symptoms
	Haloperidol 5–20	118		
Carrière et al (2000)[11]	Amisulpride 400–1200	94	16	Inpatients with paranoid schizophrenia or schizophreniform disorder
	Haloperidol 10–30	105		
Peuskens et al (1999)[14]	Amisulpride 8	115	8	Inpatients or outpatients with paranoid, disorganized, or undifferentiated schizophrenia and a minimum of positive symptoms
	Risperidone 8	113		
Sèchter et al (2002)[16]	Amisulpride 400–1000	152	51[c]	Inpatients or outpatients with paranoid, disorganized, undifferentiated, or residual schizophrenia and predominant positive symptoms
	Risperidone 4–10	158		

[a]All patients were started on the higher dose, which could then be reduced.
[b]This potentially subtherapeutic–dose group was excluded.
[c]The original trial lasted only 6 months, but there was a 12-month double-blind extension.

than the 50% BPRS score reduction criterion and because it has been developed as a standardized measure that is likely to be used in many future studies. There is no universally accepted definition of a clinically meaningful important response. Clinicians have different opinions on this matter so that they can choose the outcome that they find most clinically relevant.

There is no robust evidence as to how long an antipsychotic should be tried before response should be determined. Recent guidelines suggest waiting 3,[33] 4,[34] or 6[35] weeks before major changes in treatment are implemented. We felt that 4 weeks was a good compromise, representing a duration that is sufficiently long on the one hand, but also being acceptable by clinicians who are under pressure from patients, nurses, families, and payers to change treatment when there is insufficient response. Furthermore, not all studies had BPRS evaluations after 4 weeks, making prediction of response at later timepoints impossible.

Statistical Analysis

Percentage BPRS score reduction from baseline at 1 week and at 2 weeks were entered in a specificity, sensitivity, positive and negative predictive value analysis to predict which initial degree of nonresponse would make it likely that a patient would not respond at week 4.

As is appropriate in the development of diagnostic tests, we first calculated receiver-operator curves and the maximum Youden Index, which is a conventional measure for an optimum balance between sensitivity and specificity. Although we obtained meaningful results with sensitivities and specificities usually between 70% and 80%, the crucial measure of the positive predictive value was sometimes low. Only the positive predictive value allows one to predict how many patients with a positive test result (here a percentage BPRS score reduction at week 1 [or 2] below the cutoff identified) will not respond at week 4. Since high specificity and a high positive predictive value are more important than high sensitivity for the treatment decision as to whether the antipsychotic should be changed, we also identified the percentage BPRS score cutoff associated with 90% specificity. High specificity and a high positive predictive value are needed to avoid unnecessarily changing treatment in patients who would have responded.

It should be noted that the results obtained can be applied to both prediction of nonresponse and prediction of response. This means that if, for example, a value greater than or equal to 20% BPRS score reduction was found as the optimum cutoff for predicting response at 4 weeks, then less than 20% BPRS score reduction is the optimum cutoff for predicting nonresponse at 4 weeks. From a clinical point of view it is, however, most important to identify nonresponders as early as possible, because these are the patients who might require a change of treatment. Therefore, all results are shown on the basis of predicting nonresponse at 4 weeks. Nevertheless, since the meaning of the terms *sensitivity*, *specificity*, and *positive* and *negative predictive value* are a little confusing in an analysis trying to predict nonresponse, an explanation related to our analysis is presented in Table 2.

Finally, the following variables were entered together with the cutoffs obtained for 90% specificity in a stepwise forward logistic regression in order to analyze which of

Table 2. Explanation of Sensitivity,[a] Specificity,[b] and Positive and Negative Predictive Value[c,d] Used in the Current Study

	Negative Test Result (patient has a higher percentage BPRS score reduction from baseline than the cutoff identified)	Positive Test Result (patient has a lower percentage BPRS score reduction from baseline than the cutoff identified)
Patient is a Responder at Week 4	a	b
Patient is a Nonresponder at Week 4	c	d

[a]Sensitivity: the probability that a test is positive among all patients with the disease in the sample. In our example, it is the probability that a nonresponder at week 4 will have a percentage BPRS score reduction at week 1 (or 2) below the cutoff identified: d / (c + d).
[b]Specificity: the probability that a test is negative among all patients who do not have the disease in the sample. Here, it is the probability that a responder at week 4 will have a percentage BPRS score reduction at week 1 (or 2) that is higher than the cutoff identified: a / (a + b).
[c]Positive predictive value: the probability that a person has the disease, given a positive test result. Here, it is the probability that a patient with a percentage BPRS score reduction at week 1 (or 2) below the cutoff identified will be a nonresponder at week 4: d / (b + d).
[d]Negative predictive value: the probability that a person does not have the disease, given a negative test result. Here, it is the probability that if a patient has a percentage BPRS score reduction at week 1 (or 2) that is higher than the cutoff identified, he or she will be a responder at week 4: a / (a + c).

the following factors were independent predictors of nonresponse at 4 weeks: age, gender, body mass index, schizophrenia subtype according to DSM-III-R, duration of illness, atypical (amisulpride or risperidone) versus typical (haloperidol or flupenthixol) antipsychotic drug use, study, BPRS total score at baseline, BPRS psychotic subscore at baseline (sum of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content), and BPRS negative subscore at baseline (sum of the following items: emotional withdrawal, motor retardation, and blunted affect[36]). Please note that, according to 2 double-blind studies[14,16] and a meta-analysis,[37] the efficacy of amisulpride and risperidone is very similar, which justified pooling them in 1 group of atypical antipsychotics. Only 47 patients received flupenthixol, so we pooled these patients with haloperidol in the regression analysis.

The primary analysis was based on the observed cases at 4 weeks. In a sensitivity analysis, we used a last-observation-carried-forward approach to plot receiver-operator curves, i.e., when a patient left the study before the 4-week timepoint, his last rating was used as his endpoint.

Significance levels were set at $\alpha = .05$, 2-tailed. Data were analyzed with SPSS, version 12.0 (SPSS, Inc., Chicago, Ill.) and LogXact, version 5 (Cytel, Cambridge, Mass.).

RESULTS

Overall Response

In the completer analysis, the mean percentage BPRS score reduction from baseline to week 4 was 48.06% (SD = 29.66). We found that 79.2% of the patients fulfilled the criterion of at least 25% BPRS score reduction, 52.5% fulfilled at least 50% BPRS score reduction, and 41.4% fulfilled the remission criterion.

Sensitivity-Specificity Analyses

The results of the receiver-operator analyses to define levels of early nonresponse for predicting nonresponse at 4 weeks are summarized in Figures 1 through 6.

As expected, the most stringent nonresponse criterion, "less than 25% BPRS score reduction," was associated with lower predictive response cutoffs than "less than 50% BPRS score reduction" and "no remission." However, although more patients achieved "greater than or equal to 50% BPRS score reduction" than a "remission" at 4 weeks, the predicting percentage BPRS score reduction cutoffs were relatively similar.

When maximum Youden indices were used to identify the cutoffs providing an optimum trade-off between sensitivity and specificity, acceptable values were found for both sensitivity and specificity, roughly in a range between 70% and 80%.

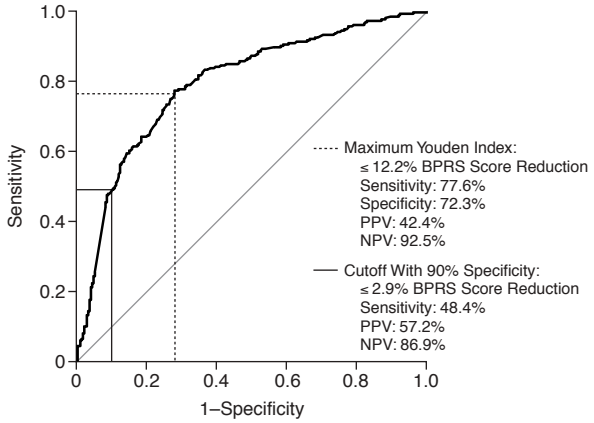
When the percentage BPRS score reduction at 1 week was used to predict response at 4 weeks, the best predictor for less than 25% BPRS reduction at week 4 was less than or equal to 12.2%, for less than 50% BPRS score reduction at week 4 was less than or equal to 18.4%, and for "no remission" at week 4 was less than or equal to 18.9%.

When the percentage BPRS score reduction at 2 weeks was used to predict response at 4 weeks, the best predictor for less than 25% BPRS score reduction at week 4 was less than or equal to 20.2%, for less than 50% BPRS score reduction at week 4 was less than or equal to 36.8%, and for "no remission" at week 4 was less than or equal to 38.0%.

Percentage BPRS score reduction at week 2 predicted nonresponse at week 4 better than percentage BPRS score reduction at week 1 because the sensitivity and specificity values were generally higher.

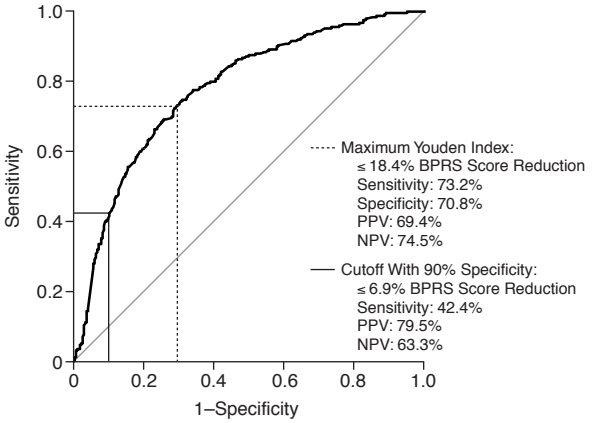
It was possible to identify cutoffs associated with 90% specificity. These were associated with lower sensitivity as must by nature be the case in an analysis of this kind. Even after this maneuver, the positive predictive values for the nonresponse definition "less than 25% BPRS score reduction at 4 weeks" remained low (57.2% for the prediction at week 1 and 63.3% for week 2). The reason for the relatively low positive predictive value is that, in contrast to sensitivity and specificity, positive predictive value depends on the incidence of the outcome, but only relatively few patients had less than 25% BPRS score

Figure 1. Receiver-Operator Curve for Prediction of < 25% BPRS Score Reduction at Week 4 by Percentage BPRS Score Reduction at Week 1



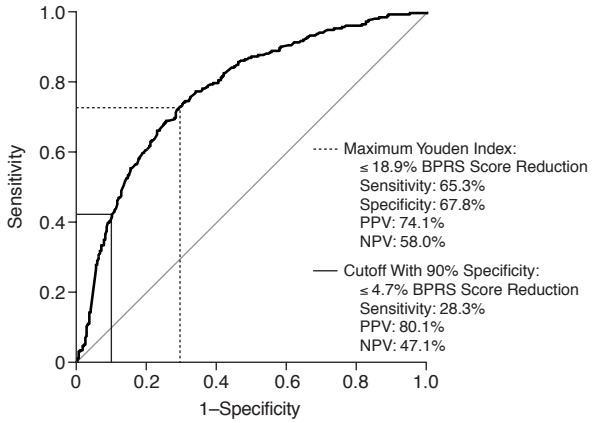
Abbreviations: BPRS = Brief Psychiatric Rating Scale, NPV = negative predictive value, PPV = positive predictive value.

Figure 2. Receiver-Operator Curve for Prediction of < 50% BPRS Score Reduction at Week 4 by Percentage BPRS Score Reduction at Week 1



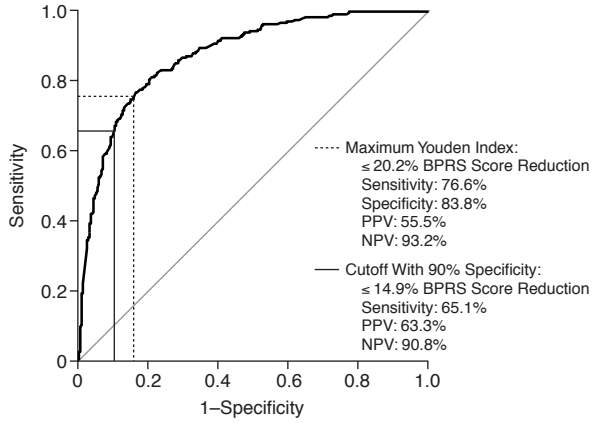
Abbreviations: BPRS = Brief Psychiatric Rating Scale, NPV = negative predictive value, PPV = positive predictive value.

Figure 3. Receiver-Operator Curve for Prediction of "Not Achieving Remission" at Week 4 by Percentage BPRS Score Reduction at Week 1



Abbreviations: BPRS = Brief Psychiatric Rating Scale, NPV = negative predictive value, PPV = positive predictive value.

Figure 4. Receiver-Operator Curve for Prediction of < 25% BPRS Score Reduction at Week 4 by Percentage BPRS Score Reduction at Week 2



Abbreviations: BPRS = Brief Psychiatric Rating Scale, NPV = negative predictive value, PPV = positive predictive value.

reduction at week 4 (304 [20.8%] of 1459 patients). To obtain a positive predictive value of at least 80%, the cutoff for the prediction at week 2 was no (0%) BPRS score reduction, while at week 1 no reliable cutoff could be identified.

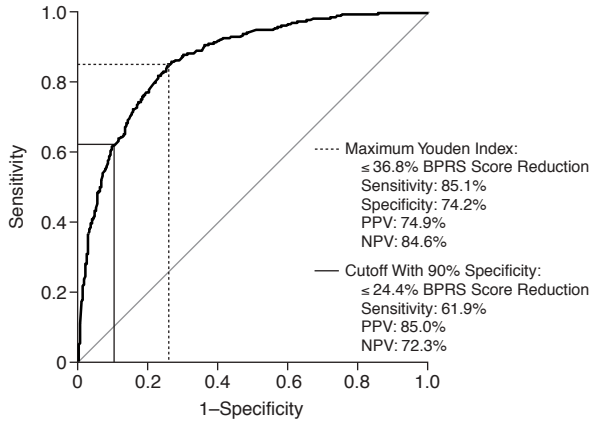
We illustrate this point in Table 2 by using the different numbers for the prediction of the primary criterion (less than 25% BPRS score reduction at 4 weeks) by percentage BPRS score reduction at 2 weeks.

The values for the cutoff derived as an optimum tradeoff between sensitivity and specificity using the Youden Index were less than or equal to 20.2% BPRS score reduction (Figure 4). The numbers according to Table 2 were a = 968, b = 187, c = 71, and d = 233. Thus, the sensitivity was 76.6% (d / [c + d]) and the specificity was 83.8% (a / [a + b]), but the positive predictive value was only 55.5% (d / [b + d]).

When the specificity was increased to 90%, the cutoff at 2 weeks was less than or equal to 14.9% BPRS score reduction, and the numbers were a = 1040, b = 115, c = 106, and d = 198. The sensitivity was 65.1%, but the positive predictive value remained relatively low (63.3%).

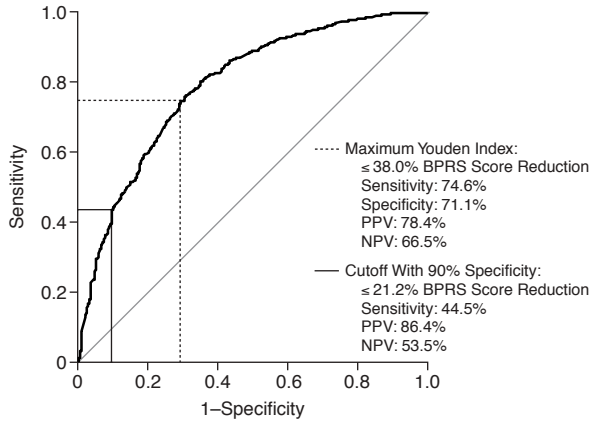
The numbers for the cutoff (0% BPRS reduction at 2 weeks) providing a positive predictive value of 80% were a = 1131, b = 24, c = 207, and d = 97. The specificity was

Figure 5. Receiver-Operator Curve for Prediction of < 50% BPRS Score Reduction at Week 4 by Percentage BPRS Score Reduction at Week 2



Abbreviations: BPRS = Brief Psychiatric Rating Scale, NPV = negative predictive value, PPV = positive predictive value.

Figure 6. Receiver-Operator Curve for Prediction of "Not Achieving Remission" at Week 4 by Percentage BPRS Score Reduction at Week 2



Abbreviations: BPRS = Brief Psychiatric Rating Scale, NPV = negative predictive value, PPV = positive predictive value.

Table 3. Cutoffs Obtained in the Last-Observation-Carried-Forward Analysis

Variable	< 25% BPRS Score Reduction at Week 4 (maximum Youden/90% specificity)	< 50% BPRS Score Reduction at Week 4 (maximum Youden/90% specificity)	No Remission at Week 4 (maximum Youden/90% specificity)
Prediction by BPRS score reduction at week 1, %	*12.28/2.99	*16.04/6.94	*16.04/5.06
Prediction by BPRS score reduction at week 2, %	*23.24/15.24	*36.56/24.47	*38.01/21.18

*The first cutoff is the optimum trade-off between specificity and sensitivity according to the Youden Index; the second is the cutoff associated with 90% specificity.
Abbreviation: BPRS = Brief Psychiatric Rating Scale.

97.9%, the sensitivity was 31.9%, the positive predictive value was 80.2%, and the negative predictive value was 84.5%.

Since only 14.3% of the patients had dropped out at 4 weeks, the cutoffs identified in the last-observation-carried-forward analysis were not markedly different from those in the observed cases. These results are summarized in Table 3.

Logistic Regression Analysis

The results of the logistic regression analyses are listed in Table 4 and can be summarized as follows:

The most important finding was that, even after controlling for the effects of other variables, the cutoffs identified by the sensitivity-specificity analyses were always the strongest factors associated with nonresponse, with odds ratios ranging between 4 and 17.

Higher age, longer duration of illness, and more symptoms at baseline were significantly associated with nonresponse at 4 weeks in some of the models. However, the odds ratios lay in a range between 0.81 and 1.06 (all ≥ 0.90, with a single exception), so that these results were statistically significant, but of limited clinical relevance. In 1 model, more positive symptoms at baseline were associated with spuriously higher response rates (odds ratio = 1.06). In 3 of 6 analyses, there were also study effects, showing that the overall response in the individual studies varied; but again, the odds ratios were close to 1 and thus of limited clinical relevance.

The use of atypical antipsychotics was associated with higher response rates compared with typical antipsychotics, and the odds ratios between 0.60 and 0.76 were more clinically meaningful than those of the other variables. Although this finding was not consistent (a significant effect was found in only 4 of 6 analyses), it reflects the modestly higher efficacy of the atypical antipsychotics amisulpride and risperidone found in the underlying studies and meta-analyses.[26,37]

DISCUSSION

The main results of our study were as follows: very roughly, the cutoffs for predicting less than 25% BPRS score reduction, less than 50% BPRS score reduction, and no remission at week 4 reflecting the optimum trade-off of sensitivity and specificity were less than 10%, 20%,

Table 4. Results of Logistic Regression Analyses

Statistically Significant Predictors	Odds Ratio	Lower 95% CI	Upper 95% CI	p Value
Prediction of < 25% BPRS score reduction at week 4 by percentage BPRS score reduction at week 1				
< 2.89% BPRS score reduction at week 1*	8.70	6.42	11.79	< .0001
Atypical vs typical antipsychotic	0.60	0.44	0.83	.0017
Age	0.99	0.97	0.999	.0388
BPRS negative subscore at baseline	0.96	0.92	0.997	.0361
Prediction of < 50% BPRS Score reduction at week 4 by percentage BPRS score reduction at week 1				
< 6.94% BPRS score reduction at week 1	6.29	4.72	8.39	< .0001
Study	0.92	0.89	0.95	< .0001
BPRS negative subscore at baseline	0.94	0.91	0.98	.0008
BPRS positive subscore at baseline	1.06	1.02	1.10	.0016
Age	0.98	0.97	1.00	.0046
Atypical vs typical antipsychotic	0.73	0.55	0.96	.0234
Prediction of "no remission" at week 4 by percentage BPRS score reduction at week 1				
BPRS negative subscore at baseline	0.90	0.87	0.94	< .0001
< 4.71% BPRS score reduction at week 1	3.77	2.75	5.18	< .0001
BPRS total score at baseline	0.97	0.96	0.98	< .0001
Atypical vs typical antipsychotic	0.76	0.58	0.99	.0456
Prediction of < 25% BPRS score reduction at week 4 by percentage BPRS score reduction at week 2				
< 14.91% BPRS score reduction at week 2	16.73	12.30	22.77	< .0001
Atypical vs typical antipsychotic	0.65	0.46	0.91	.0132
Age	0.98	0.97	1.00	.0230
Prediction of < 50% BPRS score reduction at week 4 by percentage BPRS score reduction at week 2				
< 24.38% BPRS score reduction at week 2	15.48	11.53	20.78	< .0001
Study	0.90	0.87	0.93	< .0001
Age	0.98	0.97	0.99	.0011
BPRS negative subscore at baseline	0.95	0.91	0.98	.0061
BPRS positive subscore at baseline	1.05	1.01	1.09	.0252
Prediction of "no remission" at week 4 by percentage BPRS score reduction at week 2				
< 21.18% BPRS score reduction at week 1	7.97	5.83	10.90	< .0001
BPRS total subscore at baseline	0.98	0.97	1.00	.0302
BPRS negative subscore at baseline	0.89	0.85	0.93	< .0001
BPRS positive subscore at baseline	0.93	0.88	0.97	.0035
Study	0.95	0.92	0.99	.0074
Duration of illness	0.81	0.66	0.99	.0376

*The first predictor is always the cutoff identified in the receiver-operator curves that predicted nonresponse with 90% specificity.
Abbreviation: BPRS = Brief Psychiatric Rating Scale.

and 20% at week 1, respectively. If nonresponse at week 4 was predicted by percent BPRS score reduction at week 2, the same values were roughly 20%, 40%, and 40%, respectively. The cutoffs associated with 90% specificity were virtually no response at week 1 (3%–7% BPRS score reduction) and approximately 15%, 25%, and 20%, respectively, at week 2. However, even at 90% specificity, the positive predictive value for the nonresponse criterion less than 25% BPRS score reduction was relatively low. To obtain a positive predictive value of 80% required no change in the BPRS score (0%) at week 2, whereas no reliable cutoff could be identified for week 1. In the regression analyses, the cutoffs identified were the strongest predictors of nonresponse, and the only other factor of any clinical relevance was "atypical versus typical drug use," reflecting the well-known finding that amisulpride and risperidone were modestly more effective than haloperidol in such studies.[26,37]

In contrast to earlier studies based on small samples and of correlational nature that also showed an association between early response and response at later timepoints,[4–6] our study is the first based on a large dataset of double-blind, multicenter trials that achieves quantitative estimates that may provide guidance in routine care. The only previous study with a similar design was the preliminary report by Correll et al.,[8] which was a relatively small, open-label study that was conducted in only 1 center and analyzed only 1 nonresponse criterion. Their findings were somewhat different from ours because less than 20% BPRS score reduction at 1 week predicted less than 20% BPRS score reduction at 4 weeks. The reason for this discrepancy may be that the mean percentage BPRS score reduction was lower in Correll et al.'s study. Since this study[8] involved an open 4-week trial to identify nonresponders for potential inclusion into a subsequent random assignment trial, it is conceivable that the assessments were biased toward seeing less improvement.

Strengths of our study are that we were able to use a large number of patients derived from studies that were double-blind and that were carried out in many different centers, thus enhancing the robustness and generalizability of the results. Furthermore, in contrast to many recent antipsychotic drug trials, which often included treatment-refractory participants, the patients in our database re-

sponded quite well to treatment. For example, in 2 pivotal risperidone studies in which some patients had been hospitalized at the beginning of the studies for up to 20 years,[38,39] the mean PANSS score reduction at 6 weeks was less than 20%.[40] In our set of studies, the mean percentage BPRS score reduction at 4 weeks was 48.4%. One reason for this relatively high response rate may be that all studies were carried out in Europe, in which almost all patients have health insurance, so that the problem of trial populations composed of patients who can only obtain free treatment at special centers if they participate in a study is present to a lesser extent. Nevertheless, even in our dataset, it is likely that there were many relatively poor drug responders who entered clinical trials in the hope of finding a new effective treatment. Such patients would bias the results toward lower overall response. We were not confronted with the enormous problem of very high dropout rates in recent antipsychotic drug trials that often reach 50% even in the short run[41]; only 14.6% of the patients had dropped out at 4 weeks. This also explains why our sensitivity analysis using a last-observation-carried-forward approach did not yield findings that differed to any important extent. Finally, since there is no unanimously accepted criterion of (non) response, we analyzed 3 different criteria, 1 reflecting minimal improvement according to clinicians' judgment (25% BPRS score reduction[31]), 1 reflecting much improvement (50% BPRS score reduction[31]), and a third that has recently been introduced as a remission criterion for schizophrenia.[28] Clinicians can thus choose the criterion that is appropriate for their needs.

A number of limitations must be discussed. Nonresponse was assessed only after 4 weeks. Although a substantial part of the overall antipsychotic drug effect seems to occur within the first 4 weeks of treatment, there are of course patients who will respond only later.[2] Nevertheless, in clinical routine, there comes a time when treatment must be changed, and given the pressure from patients, relatives, and insurance companies, keeping patients on the same antipsychotic for 4 weeks may mean quite a long wait for many clinicians.

We did not make a selection among studies but rather used all studies of patients in the amisulpride database with positive symptoms. Although the studies differed in some aspects of design, we found no obvious reasons why certain studies should be more appropriate to our question than others. In some of the regression analyses, there were indeed statistically significant study effects, but the size of the effect was small ($0.90 \leq$ odds ratios < 1.00). The most important difference may be that some studies used a fixed-dose design and others a flexible one. However, with only 1 exception,[10] the flexible-dose studies started with a high-loading dose (see Method section) so that the patients received a sufficient dose right from the start in these studies as well. A post hoc sensitivity analysis of the nonresponse criterion less than 25% BPRS score reduction excluding the 1 study[10] in which slower titration was possible did not change the receiver-operator curves to any relevant degree (this was also the only open study). In clinical practice, some physicians start with the full dose of an antipsychotic the first day, while others titrate antipsychotics more slowly; this justifies the pooling of the studies. Nevertheless, since titration is mandatory for some antipsychotics, we believe that 2 weeks is a more realistic time for the first assessment of response and thus consider our 2-week results to be more clinically relevant.

Despite the large sample size, the generalizability of our results may be reduced by the strict inclusion and exclusion criteria of the studies (e.g., exclusion of suicidal patients or of patients with substance abuse). A replication by more naturalistic studies is needed. The challenge of such studies will be to recruit numbers of cases that are large enough to allow robust findings.

Our database included only the antipsychotics amisulpride, risperidone, haloperidol, and flupenthixol. Thus, replications with other atypical antipsychotics would also be useful, although the effect sizes found in meta-analyses do not suggest great efficacy differences between available antipsychotics.[37] Given the small efficacy differences between available antipsychotic drugs, we also feel that the pooling of so-called atypical and typical antipsychotics in our analysis was justified. Indeed, the logistic regression analyses showed only moderate and inconsistent effects in terms of atypical versus typical drugs. For the same reason, we think it is not a major problem that amisulpride, which contributed about 60% of the included patients, is not available in the United States. There are no data suggesting that the time course pattern of different antipsychotics is substantially different.

Last but not least, the finding that patients who have shown little response at week 2 are unlikely to respond to the same drug at week 4 does not necessarily imply that an early switch of the antipsychotic increases their likelihood to respond. Only studies randomizing nonresponders after 2 weeks to either continuation with the same drug or switching to another drug can elucidate this issue. We believe that our results call for studies of such a design, similar to those reported by Kinon et al.[42] for nonresponders at 4 weeks.

Drug names: haloperidol (Haldol and others), risperidone (Risperdal).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, amisulpride and flupenthixol are not approved for use in the United States.

Financial disclosure: In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME article were asked to complete a statement regarding all relevant financial relationships between themselves or their spouse/partner and any commercial interest (i.e., any proprietary entity producing health care goods or services consumed by, or used on, patients) occurring

within at least 12 months prior to joining this activity. The CME Institute has resolved any conflicts of interest that were identified. The disclosures are as follows: Dr. Leucht has received speaker or consultancy honoraria from SanofiAventis, Bristol-Myers Squibb, Eli Lilly, Janssen, Lundbeck, and Pfizer and has obtained research support from Eli Lilly, Lundbeck, and Johnson & Johnson. Dr. Kissling has received speaker or consultancy honoraria from SanofiAventis, Bristol-Myers Squibb, Eli Lilly, Janssen, Lundbeck, Bayer, and Pfizer. Dr. Kane is a consultant for Pfizer, Abbott, Eli Lilly, Janssen, and Bristol-Myers Squibb and has received honoraria from Bristol-Myers Squibb and Janssen. Ms. Busch has no personal affiliations or financial relationships with any proprietary entity producing health care goods or services consumed by, or used on, patients to disclose relative to the article.

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