Early Perception of Medication Benefit Predicts Subsequent Antipsychotic Response in Schizophrenia: "The Consumer Has a Point" Revisited

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Abstract

Background: An easy-to-administer tool for predicting response to antipsychotic treatment could improve the acute management of patients with schizophrenia. We assessed whether a patient's perception of medication benefit early in treatment could predict subsequent response or nonresponse to continued use of the same treatment. **Method:** This post hoc analysis used data from a randomized, open-label trial of antipsychotics for treatment of schizophrenia in which attitudes about medication adherence were assessed after two weeks of antipsychotic treatment using the Rating of Medication Influences (ROMI) scale. The analysis included 439 patients who had Positive and Negative Syndrome Scale (PANSS) and ROMI scale data at Weeks 2 and 8. Scores on the ROMI subscale Perceived Medication Benefit factor were used to predict subsequent antipsychotic response at Week 8, defined as a ≥20% reduction from baseline on the PANSS. Logistic regression was used to identify a cut-off score for the Perceived Medication Benefit factor that could accurately identify antipsychotic responders vs. nonresponders at Week 8. **Results:** A score of ≥2.75 (equal to a mean subscale score of ≥11.00) on the ROMI scale Perceived Medication Benefit factor at Week 2 predicted response at Week 8 with high specificity (72%) and negative predictive value (70%), moderate sensitivity (44%) and positive predictive value (47%), and with a 38% misclassification rate. **Conclusions:** A brief assessment of the patient's perception of medication benefit at two weeks into treatment appears to be a good predictor of subsequent response and nonresponse after eight weeks of treatment with the same antipsychotic.

Key Words: Adherence, Antipsychotics, Predictors, Rating Instruments, Schizophrenia

Introduction

Over thirty years ago, in an effort to identify factors that led patients with schizophrenia to refuse medication, Van Putten and May (1) and Van Putten et al. (2) found that a patient's subjective response to a test dose of antipsychotic medication was highly predictive of subsequent clinical response and adherence to treatment. Subjective response was assessed using four simple questions: How does the medication agree with you? Did it make you feel calmer? Did it affect your thinking? Do you think this would be the right medicine for you? In addition to subjective benefits predicting favorable response, subjective distress over side effects—particularly subjective extrapyramidal symptoms (EPS) and drowsiness—was identified as a predictor of poor response and medication refusal.

The Van Putten studies were done with antipsychotics available at the time, well before the arrival of clozapine and other second-generation antipsychotics. In these studies, adverse subjective response often correlated with EPS, especially akathisia and akinesia, which were hypothesized to be the primary "drivers" of poor antipsychotic response (3). With the advent of atypical antipsychotics, the occurrence of

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Clinical Implications

In this analysis we created a model for predicting nonresponse to antipsychotic medication after eight weeks of treatment in which the clinician, after following two weeks of treatment, can ask a patient with schizophrenia four simple questions regarding his view of whether the new medication was beneficial. This model performed with high specificity and a robust negative predictive value, the two characteristics most important in allowing clinicians to confidently identify those patients at risk for subsequent poor response. These findings have important clinical implications. The model developed here provides clinicians with a simple assessment tool that can be quickly administered at a single point in time, providing results that may enable rapid identification of patients who are unlikely to do well in the longer term if their treatment strategy is not modified. Early modification of treatment—a different drug, a different dose, or a different delivery method—could limit patient exposure to ineffective treatment and the recognized side effects and idiosyncratic responses attendant with treatment of any kind.

EPS has greatly diminished (4, 5), but the problem of poor response remains. Nearly two-thirds of patients with moderate to severe symptoms fail to show moderate improvement after three months of therapy (6, 7). For many years, clinicians allowed between four and eight weeks for an antipsychotic to take full effect prior to altering a patient's treatment regimen. It is now widely accepted that beneficial treatment effects should occur within one (8) to two (9) weeks of treatment initiation, oftentimes within the first 24 hours (10), and that the majority of overall long-term improvement occurs in the first two to four weeks (9, 11). This finding has led to a search for early response parameters that can be used to guide clinicians in reacting to lack of clinical improvement in a way that minimizes exposure to ineffective treatment strategies while avoiding a premature change in course.

Recent research has shown that failure to demonstrate early improvement on a given therapy—as measured by change in symptom rating scales such as the Positive and Negative Syndrome Scale (PANSS) (12) and the Brief Psychiatric Rating Scale (BPRS) (13)—predicts subsequent poor response to continued use of the same therapy (6, 7, 14-16). Typically, a change in score from baseline to Week 2 of treatment was used to predict outcome at Week 8 or beyond. Although these findings have important implications for early medical management of schizophrenia, they have yet to be applied in "real world" practice settings, where time constraints limit use of symptom rating scales.

Thirty-plus years beyond Van Putten's initial observation, the landscape of schizophrenia treatment has changed. There have been significant shifts in treatment setting from inpatient to outpatient, and changes in antipsychotic prescribing, with a predominance of newer antipsychotic medications that generally have less EPS burden than those used in the Van Putten studies. Relatively little is known about whether, in this environment, a patient's initial subjective assessment of his antipsychotic medication predicts subsequent medication response. To address this question, we have assessed early subjective response to antipsychotic medication using a subscale of the Rating of Medication Influences (17) (ROMI) scale. The ROMI is a brief, standardized assessment of attitudinal and behavioral factors that influence medication adherence and nonadherence. The full ROMI covers a wide range of adherence influences, not all of which address direct subjective response to medication. One of the ROMI factor subscales—the Perceived Medication Benefit factor—measures subjective response to medication (18). It is a 4-item factor that has been significantly associated with improvement in the positive symptom and disorganized thought domains of the PANSS (19).

The ROMI is not the only patient-reported measure to assess patients' subjective perceptions of their antipsychotic medication therapy. The Subjective Well-Being under Neuroleptics (SWN) (20), a 30-item scale, and its shortened 20-item version (SWN-S) (21), assess patients' subjective well-being of treatment with antipsychotics and have been found to predict later remission, adherence, and symptomatic and functional improvement (20-22). Another measure of patients' perceptions of medication benefit, the 10-item Drug Attitude Inventory (DAI) (23), was also found to predict adherence to drug therapy and subsequent clinical improvement (24, 25) as measured by the PANSS.

In this post hoc analysis of data from a 1-year, randomized, open-label trial, which included the ROMI, we assess the potential for the ROMI Perceived Medication Benefit factor score at Week 2 of treatment to predict clinical outcome at Week 8. Predictive characteristics generated with this approach are compared to those of two previously reported prediction models: one utilizing patients' early scores (Week 2) on the complete 30-item PANSS (26) and the other using an abbreviated, 6-item assessment of early (Week 2) scores on PANSS positive symptoms (27).

Method

Data were drawn from a 1-year, randomized, open-label study of the cost-effectiveness and functional outcomes associated with treatment of schizophrenia using olanzapine (Eli Lilly and Company; Indianapolis, Indiana, USA), risperidone (Ortho-McNeil-Janssen Pharmaceuticals, Inc.; Raritan, New Jersey, USA), and conventional antipsychotics in usual clinical practice (28).

Patients

Enrolled patients were ≥18 years of age, of either gender, mainly outpatients (95%), and diagnosed with schizophrenia (64%) or schizoaffective disorder (34%) based on *DSM-IV* criteria. All patients met a psychotic symptom threshold of ≥18 on the BPRS (based upon a 0–6 normalized rating scale). Excluded were patients with very serious, unstable physical illness and those with contraindications to any of the study medications. The study protocol was approved by individual institutional review boards and the principal investigator and staff at each study site underwent extensive training in the administration of the PANSS and the ROMI prior to enrolling any patients. All patients provided written informed consent before receiving any study therapy or procedures. Initial dosing, titration, and dosing adjustments were determined by the attending clinician. While the study had an effectiveness orientation, investigators and patients were encouraged to continue with the initial antipsychotic therapy for at least eight weeks, barring any significant adverse event. After the initial eight weeks, antipsychotic switching was permitted as per clinical judgment. During the 12-month follow-up, 83.6% of patients experienced switching of antipsychotic medications at least once. Simultaneous use of two antipsychotic agents was permitted only during the interval required to safely transition from one to another. Clinical and resource utilization data were collected at baseline and at five post-baseline visits (2, 8, 20, 32, and 48 weeks). Only data collected at baseline and at Weeks 2 and 8 were used in the current analysis.

Measurement of Patient Perception of Medication Benefit and Symptom Severity

Perception of Medication Benefit was quantified using the ROMI scale, a standardized measure of attitudinal and behavioral factors that influence whether a patient adheres to treatment (17). It consists of nine statements that reflect potential reasons for adherence and ten statements that reflect potential reasons for nonadherence. Patients are asked to indicate their level of agreement with each statement on a 3-point scale: strong=3, mild=2, or none=1. Prior research on the psychometric properties of the ROMI—including inter-rater reliability, internal consistency, principal components, and correlations with other established measures like the DAI—has found it to be a valid and reliable measure of attitudes and behaviors influencing patient adherence with antipsychotic therapy (17).

In the initial ROMI publication, seven main factors of the ROMI scale were identified: Perceived Medication Benefit, Positive External Influence, Denial of Medication, Outside Opposition, Negative Aspects of Medication, Substance Abuse, and Treatment Access (18). Since then, the ROMI has been widely used as a measure of adherence attitudes, but the specific predictors have varied by study. The ROMI items used in the current analysis constitute the "Perceptions of Medication Benefit factor" and represent the average of scores from the following four ROMI statements: perceived daily benefit (Do you believe the medicine helps you feel better?); fear of relapse (Do you believe taking the medicine prevents your illness or symptoms from returning?); side effect relief (Compared with other medicines, does this one have fewer side effects, so it is easier for you to stay on?); and, fulfillment of life goals (Do you feel that this medication helps you to achieve certain goals or life aspirations?). This ROMI factor has been found to be a robust predictor of treatment duration in the antipsychotic therapy of schizophrenia patients, and higher scores on this factor were significantly correlated with better clinical psychopathology and better quality of life and well-being (19). Although further research is needed to assess the validity and reliability of this factor scale of the ROMI as a standalone measure, available research suggests that the Perceptions of Medication Benefit factor scale has construct validity.

Symptom severity was measured using the PANSS (12)—a rating instrument to evaluate the presence and severity of positive, negative, and general psychopathology—consisting of thirty items, each scored from 1 (absent) to 7 (severe). Based on previous studies of early response predicting later response (26), we defined response to treatment as a ≥20% reduction from the baseline PANSS Total score following eight weeks of therapy.

Statistical Analyses

The current analyses included patients who had ROMI scores at Week 2 and PANSS scores at both Week 2 and Week 8 (n=439 of 664 enrolled patients, 66%). In preliminary analyses, we employed logistic regression analysis to identify elements of the ROMI at Week 2 that were associated with symptomatic outcome at Week 8. During initial exploration of a multivariate model, a strong association between the Perceived Medication Benefit factor score at Week 2 and Week 8 outcome was identified. For simplicity, this factor was used as a lone predictor in the final model. The optimal threshold for this factor was determined by examining the predictive characteristics of all possible values for this factor, and the best fitting threshold score was 2.75 (equal to a mean subscale score of 11.00). Patients with scores ≥2.75 were identified as likely responders at Week 8 and those with scores <2.75 were identified as likely nonresponders. A rating of ≥2.75 results from expressing "Strong Agreement" on at least 3 of the 4 ROMI items, and at least "Mild Agreement" on 1 item.

The power to predict response or nonresponse at Week

8 using a threshold value of 2.75 for the ROMI Perceived Medication Benefit factor score at Week 2 was characterized using sensitivity, specificity, positive predictive value (PPV; the proportion of patients who were responders at 8 weeks among those classified as responders at 2 weeks), and negative predictive value (NPV; the proportion of patients who were nonresponders at 8 weeks among those classified as nonresponders at 2 weeks). Of these values, NPV is of greatest clinical interest because changes in medical management are most often targeted to those who are not responding to treatment. In addition, we calculated the rate of misclassification; that is, the sum of the likelihoods that individuals identified as early responders would later fail to respond, and that those identified as early nonresponders would meet criteria for response at Week 8. To assess the sensitivity of this model, we reproduced these measures using Perceived Medication Benefit score cut-offs of 2.00 and 3.00 (equal to mean subscale scores of 8.00 and 12.00, respectively).

To place the predictive characteristics derived using the ROMI factor model in context, we analyzed the dataset using two previously identified predictors, hereafter referred to as the Complete PANSS model and the Abbreviated PANSS model. In the Complete PANSS model, patients are identified as likely responders or nonresponders at Week 8 based on a reduction of ≥20% or <20%, respectively, in the PANSS Total score at Week 2. This method was derived from the same dataset used to develop the model under consideration here, and involves administering the complete 30-item PANSS at baseline, Week 2, and Week 8 (26). The Abbreviated PANSS model uses only six PANSS items. If patients show a ≥2 unit drop in 2 or more of 5 psychotic items (delusion, conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) at Week 2, they are predicted to be responders at Week 8. For patients not meeting this first criterion, a >2-unit drop or <2-unit drop in the PANSS excitement item at Week 2 is used to identify those patients likely to be nonresponders and those whose outcome is indeterminate, respectively (27). This model was derived from classification and regression tree (CART) analysis in which data from six large antipsychotic comparator trials (not including the dataset used here) were pooled and used to develop a set of rules for dividing a large heterogeneous population into smaller, more homogeneous groups with respect to outcome (29)

Results

Patient Characteristics and Illness Severity

Of the 664 patients who participated in the randomized, open-label trial, 439 (66%) had ROMI scores at Week 2 and PANSS scores at both baseline and Week 8, and were, therefore, included in this analysis. Of these patients, 163 were randomized to olanzapine, 138 to risperidone, and 138 to conventional antipsychotic treatment. Patients who were included in the current analysis were similar to patients who were excluded on a host of baseline demographic and clinical characteristics (i.e., gender, race, marital status, level of education, being employed, age at first hospitalization, number of past schizophrenia episodes, inpatient status, and level of insight per PANSS insight item). However, compared to those excluded from the analysis, the included patients were significantly older (43.5 vs. 41.3 years, p=0.027) and had a lower level of PANSS Total score (85.5 vs. 89.4, p=0.012).

Using Week 8 criteria for response, 36% (156/439) of patients were identified as responders and 64% (280/439) were identified as nonresponders. Patients had an average age of 43.5 years (standard deviation [SD]=12.0) and the majority (62%) were of male gender. Race was reported as white by 57% (250/439) of patients and as African American by 32% (140/439) of patients. Although 28% of patients had been hospitalized in the previous year, most (95.4%) were outpatients at the start of the study. Health insurance was held by 85% (373/439) of patients. The mean age at first psychiatric hospitalization was 25.8 (SD=9.2) years and the mean duration of illness was 21.3 (SD=12.2) years. Patients had a 41% lifetime prevalence of a substance use disorder, and tardive dyskinesia was present in 18% at baseline.

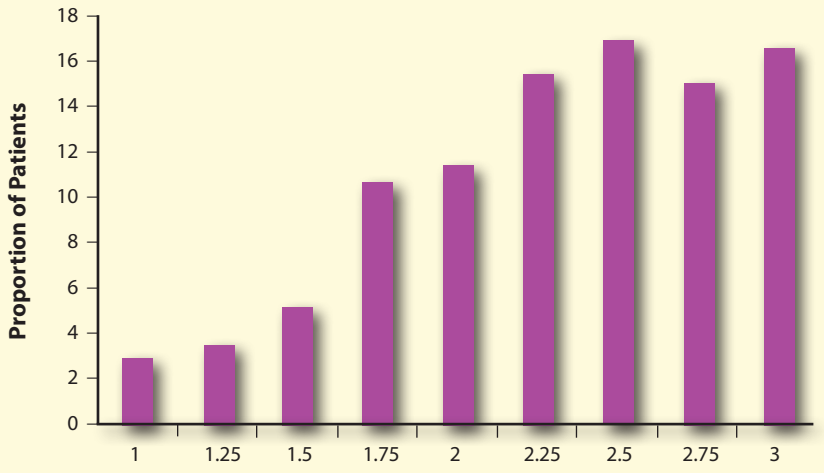
Mean PANSS Total scores and subscores (Positive, Negative, General Psychopathology) at baseline, Week 2, and Week 8 are shown in Table 1. The mean PANSS Total score at baseline was 85.5 (SD=20.6), suggesting that these chronically ill patients had active symptoms of schizophrenia that were likely to be distressing or disruptive to the patient and others. As measured using the PANSS, illness severity had improved by Week 2 and improved further by Week 8.

Table 1 Mean PANSS Total Score, Positive Score, Negative Score, and General Psychopathology Score for Patients at Baseline, Week 2, and Week 8

	In Treatment		
Score, mean (SD)	Baseline	Week 2	Week 8
PANSS Total	85.5 (SD 20.6)	76.2 (SD 19.9)	72.0 (SD 19.7)
PANSS Positive	20.1 (5.7)	17.7 (5.7)	16.4 (5.5)
PANSS Negative	22.4 (7.0)	20.3 (6.8)	19.3 (6.6)
PANSS General Psychopathology	43.0 (11.3)	38.2 (10.7)	36.3 (10.5)

PANSS=Positive and Negative Syndrome Scale; SD=standard deviation.

Figure 1 Proportion of Patients with Various Mean Item Scores for the ROMI Scale Perceived Medication Benefit Factor Scores at Week 2



ROMI=Rating of Medication Influence.

Perceived Medication Benefit Factor Model

Figure 1 illustrates the distribution of Perceived Medication Benefit factor scores at Week 2 of therapy for the study population. Roughly 3 in 4 patients (334/439, 76%) had a score of between 2.00 and 3.00 (equal to a mean subscale score of 8.00 to 12.00, respectively), reflecting mild to strong agreement with the four statements comprising this factor.

Table 2 shows the predictive characteristics for the model of Perceived Medication Benefit factor score at Week 2 predicting PANSS Total score at Week 8. Results are shown for the threshold factor score of ≥2.75 (equal to a mean subscale score of ≥11.00), which was found through assessment of all possible scores to most accurately distinguish those patients who were and were not likely to respond at Week 8, and for greater and lesser threshold scores used in the sensitivity analysis. The probability that a nonresponder at Week 8 would have had a score <2.75 was 77% (high specificity) and the probability that a patient with a score <2.75 would be a subsequent nonresponder was 70% (high NPV). The probabilities that a responder at Week 8 would have had a Perceived Medication Benefit score ≥2.75 or that patients with scores of ≥2.75 would subsequently respond at Week 8 were less robust (sensitivity=44%; PPV=47%). The lower threshold of 2.00 (equal to a mean subscale score of 8.00) used in the sensitivity analysis resulted in considerably greater sensitivity (87% vs. 44%), but at the cost of more frequent misclassifications (54% vs. 38%).

Table 2 Predictive Characteristics for the ROMI Scale Perceived Medication Benefit Factor Score at Week 2 of Treatment Predicting PANSS Total Score at Week 8

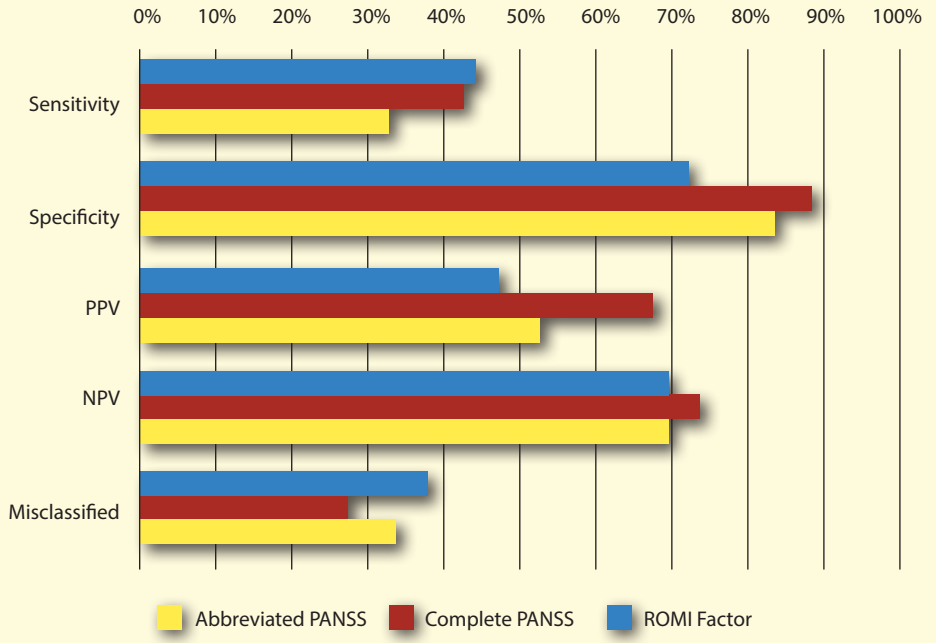
	Level of Agreement with Statements Included in the ROMI Scale Perceived Medication Benefit Factor		
	Mild (Score=2.00)	Mild to Strong (Score=2.75)*	Strong (Score=3.00)
Sensitivity	87%	44%	28%
Specificity	23%	72%	85%
PPV	39%	47%	50%
NPV	77%	70%	68%
Misclassified	54%	38%	36%

NPV=negative predictive value; PPV=positive predictive value; ROMI=Rating of Medication Influence. *Results are shown for the factor score identified as the optimal threshold (2.75; double boxed) based on CART analyses, and from flanking values (scores=2.00 and 3.00) used to test the validity of the model.

Comparisons of Predictive Models

In Figure 2, the predictive characteristics of the Perceived Medication Benefit factor model are shown alongside those of previously used predictive models: the Complete PANSS model and the Abbreviated PANSS model. The patient-centered Perceived Medication Benefit factor model compared reasonably well to the two symptom-based mod-

Figure 2 Predictive Characteristics for ROMI Factor Model*, Complete PANSS Model†, and Abbreviated PANSS Model‡



NPV=negative predictive value; PANSS=Positive and Negative Syndrome Scale; PPV=positive predictive value; ROMI=Rating of Medication Influence. *Based on the Perceived Medication Benefit factor score of the ROMI scale (cut-off=2.75 [equal to a mean subscale score of 11.00]); †Based on a >20% improvement from baseline to Week 2 in PANSS Total score; ‡Based on a Classification and Regression Tree-derived algorithm involving 6 PANSS Positive factor scores.

els. Although the specificity and PPV were lower, the NPV was equivalent to that of the Abbreviated PANSS model, and the present model had greater sensitivity than that seen with either of the two previously described models.

Discussion

In this analysis, we have demonstrated that a simple model based on patient response to 4 questions concerning perceived medication benefit after two weeks of treatment can predict subsequent nonresponse to treatment. Based on a ROMI Perceived Medication Benefit factor scale threshold score of ≥2.75 (equal to a mean subscale score of ≥11.00), not all patients who respond at Week 8 had a Week 2 score above threshold, but having a Week 2 score beneath threshold was highly predictive of later nonresponse.

Within the current dataset, both the Complete PANSS model and the Abbreviated PANSS algorithm produced somewhat better predictive values compared to the Perceived Medication Benefit factor model (cut-off score of 2.75 [equal to a mean subscale score of 11.00]). However, both the Complete PANSS and the Abbreviated PANSS require clinician training and repeated administration. Additionally, the Complete PANSS is time consuming to administer, generally taking between 40 and 60 minutes to complete. The model developed here is unique in its ease of assessment and reliance on patient self-assessment. When used in conjunction with clinical expertise, the predictive value of this tool could increase substantially. Likewise, other variables such as insight into illness, a factor that has previously been shown to be predictive of outcome (30), might have additive value in identifying patients at risk for poor response. Further research into the systematic use of these predictors is needed.

These findings have important clinical implications. The model developed here provides clinicians with a simple assessment tool that can be quickly administered at a single point in time, providing results that may enable rapid identification of patients who are unlikely to do well in the longer term if their treatment strategy is not modified. Early modification of treatment—a different drug, a different dose, or a different delivery method—could limit patient exposure to ineffective treatment and the recognized side effects and idiosyncratic responses attendant with treatment of any kind.

Our results echo those of Van Putten et al. (1), who

developed a 4-question, simple assessment of subjective response to antipsychotic medication, and found that answers to these questions after 4, 24, and 48 hours of treatment correlated with symptomatic improvement in response to chlorpromazine prior to discharge (on average, 6 weeks later). Using the same 4-question assessment tool, he later found that in 63 patients newly admitted with schizophrenic illness, an unfavorable subjective response in the first several days following a test dose of thiothixene was strongly correlated with early and eventual refusal. In that study, he noted that patients with poor subjective response were less symptomatic prior to the test dose and had greater EPS following the test dose. For patients with poor subjective response, a good outcome was more likely when small doses of medication had been used (2).

These findings have important clinical implications. The model developed here provides clinicians with a simple assessment tool that can be quickly administered at a single point in time, providing results that may enable rapid identification of patients who are unlikely to do well in the longer term if their treatment strategy is not modified.

In this report, comparisons were made to predictive models that used the complete 30-item PANSS and an abbreviated version derived using CART analysis, which is not to say that the scales were similar; but, rather, to place the predictive characteristics derived using the ROMI factor model in context with symptom-based predictive models. The similarity between the predictive characteristics for both PANSS-based models as applied to this dataset and as originally reported was quite good. The dataset used in the current study to develop the ROMI Perceived Medication Benefit model was drawn from the larger study used to create the Complete PANSS predictive model. For this reason, the predictive values derived from application of these models to the current dataset are very similar. Predictive values reported in association with publication of the Abbreviated PANSS model were similar with respect to NPV (70% and 75%, respectively), but PPVs differed (53% and 79%, respectively) (27). A reason for this discrepancy might be found in the much smaller sample size of the current study compared with the initial PANSS early response algorithm study (n=439 and n=1,494, respectively). The link between these two symptom-based predictive models and the model based on Perceived Medication Benefit is likely patient insight, considering the moderate correlation found between patients' attitudes toward antipsychotic medication and insight, and between symptom severity and insight (31, 32).

Results presented here are exploratory in nature and in need of replication. Interpretation of this study is limited by the fact that this is the first report of a prediction model based on the ROMI scale. For this study, ROMI scale scores at baseline were not available, and yet it is likely that a patient's anticipation of benefit might significantly affect long-term outcome. The correlation between subjective response four hours after a test dose and long-term outcome seen by Van Putten may reflect anticipatory benefit more than drug effect. Prospective studies are needed to address this limitation. Of the 664 patients in the primary dataset, 439 (66%) had completed both time point assessments with ROMI and PANSS. Despite similarities on many baseline demographic parameters and clinical characteristics, the patients excluded due to missing data were found to differ from those included in this analysis on age and illness severity, thus impacting study findings in an unknown manner. Finally, a ≥20% reduction from baseline in PANSS Total score has been correlated to minimal improvement on the Clinical Global Impression-Improvement scale (33). This modest threshold for defining response at Week 8 may have been too small to be clinically meaningful.

In conclusion, in this analysis we created a model for predicting nonresponse to antipsychotic medication after eight weeks of treatment in which the clinician, after following two weeks of treatment, can ask a patient with schizophrenia four simple questions regarding his view of whether the new medication was beneficial. This model performed with high specificity and a robust NPV, the two characteristics most important in allowing clinicians to confidently identify those patients at risk for subsequent poor response. The successful development of a prediction model that is simple to implement may allow for its translation into everyday clinical practice, and lends support to Van Putten's original thesis, that yes, indeed, the consumer may have a point.

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