

Clinical, Functional, and Economic Ramifications of Early Nonresponse to Antipsychotics in the Naturalistic Treatment of Schizophrenia

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Objective: Early nonresponse to antipsychotics appears to predict subsequent nonresponse to treatment when assessed in randomized controlled trials of predominately acute inpatients treated for schizophrenia. This study assessed the predictive accuracy of early nonresponse to treatment and its clinical, functional, and economic ramifications in the naturalistic treatment of predominately chronic outpatients treated for schizophrenia. **Methods:** This post hoc analysis used data from a 1-year, randomized, open-label study of olanzapine, risperidone, and typical antipsychotics in the treatment of schizophrenia. If clinically warranted, patients could switch antipsychotics following 8 weeks of treatment. Patients completing 8 weeks of treatment ($n = 443$ of 664 enrollees) were included. Patients with early response ($\geq 20\%$ improvement from baseline on the Positive and Negative Syndrome Scale at 2 weeks) were compared with early nonresponders on symptom remission, functionality, perceptions of medication influence, and total health care costs at 8 weeks. **Results:** Early response/nonresponse at 2 weeks predicted subsequent response/nonresponse at 8 weeks with a high level of accuracy (72%) and specificity (89%). After 8 weeks, early nonresponders were less likely to achieve symptom remission ($P < .001$), improved less on functional domains ($P < .05$), perceived medication as less beneficial ($P = .004$), and incurred total health care costs over twice that of early responders (\$4349 vs \$2102, $P = .010$). **Conclusions:** In the usual care of schizophrenia patients, early nonresponse appears to reliably predict subsequent nonresponse to continued treatment with the same medication to be associated with poorer outcomes and higher health care costs. Identifying early nonresponders

may minimize prolonging exposure to suboptimal or ineffective treatment strategies.

Key words: psychosis/outcome/improvement prediction

Introduction

Clinicians have long believed in a delayed onset of the action of antipsychotic drugs and assumed there is a need to reassess the choice of an antipsychotic only after 4–8 weeks of treatment.^{1–6} This “delayed onset” hypothesis was questioned long ago,⁷ but interest in formally testing this hypothesis was recently rekindled by a meta-analysis⁸ of 42 controlled randomized clinical trials (RCTs) in the treatment of predominately acutely ill inpatients with schizophrenia. This meta-analysis found that a larger reduction of symptoms occurs during the first 2 weeks than during the rest of the 4-week treatment period with the same antipsychotic agent. Additional post hoc analyses of RCT data in the treatment of predominately acute inpatients with schizophrenia^{9–11} have also shown that early nonresponse—as early as 1 or 2 weeks—can reliably predict subsequent nonresponse to treatment of schizophrenia with antipsychotics.

Most prior research has used data from subjects enrolled in randomized, double-blind, clinical trials that differ substantially from those treated with open label in routine care.¹² RCTs typically exclude subjects with comorbid disorders, especially comorbid substance abuse and medical conditions, and often account for less than 14% of all schizophrenic patients in the same clinical facilities.¹³ Furthermore, previous studies^{9–11,14} were initiated at inpatient settings, thus, possibly confounded by nonspecific effects of hospitalization during the initial phases of the studies.¹⁰ The authors themselves have noted such limitations leading to an inability to generalize these findings to patients treated in routine outpatient settings. Thus, if findings from RCTs with acutely ill inpatients can be replicated in the usual treatment of chronically ill outpatients with schizophrenia, the generalization of the findings may have important clinical, functional, and economic implications for the treatment

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of patients with schizophrenia in outpatient clinical practice, including enhancement of clinicians' ability to limit prolonged exposure to subtherapeutic or ineffective antipsychotic treatment regimens.

To address this scientific gap and expand prior research to chronically ill outpatients treated in a usual care setting, we performed a post hoc analysis using data from a practical, randomized, open-label, multisite, naturalistic study of antipsychotics in the treatment of schizophrenia in the United States that had broad inclusion criteria and did not exclude patients with comorbid medical or psychiatric conditions. We first calculated conditional probabilities—as did prior studies^{9–11}—to examine whether early response/nonresponse to antipsychotic medication (at 2 weeks of treatment) accurately predicts subsequent response to treatment (following 8 weeks of treatment). We aimed to assess whether previously reported findings, using data from double-blind trials with predominately acutely ill inpatients, can be replicated when treatment is open label and is provided to predominately chronically ill outpatients. We used 2 response criteria, a relative and an absolute response criterion, because relative response criteria are vulnerable to the effect of baseline scores. We then compared early responders and early nonresponders on subsequent clinical, functional, and economic outcomes after 8 weeks of continued therapy with the same antipsychotic agents.

Methods

Participants

Data for this post hoc analysis were drawn from a 1-year, Lilly-sponsored, practical, randomized, open-label, multisite, cost-effectiveness study ($N = 664$) of olanzapine, risperidone, and typical antipsychotics in the treatment of schizophrenia (HGGD). The primary results of this study were previously published.¹⁵ Participants were at least 18 years old meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder and met a symptom threshold of 18 or more on the Brief Psychiatric Rating Scale¹⁶ derived from the Positive and Negative Syndrome Scale (PANSS).¹⁷ In order to enhance generalizability of study results to treatment in usual care settings, the study inclusion criteria were broad allowing enrollment of subjects with substance abuse or other psychiatric and medical comorbidities, unless the condition was very serious and needed immediate attention. Enrollees were chronically ill individuals; almost all outpatients (95%) who were deemed by their treating physicians to require a medication change primarily due to poor efficacy of prior medication. A few participants were also eligible to enroll in the study if a treatment change was required due to

medication intolerability. Participants had about 17 years since first psychiatric hospitalization, and their illness severity was at least moderately severe as indicated by the moderately high PANSS total score (mean 86.9, $SD = 19.8$).¹⁸ About one-third of the sample (31%) had a psychiatric hospitalization in the past year, and most were unemployed (81%).¹⁵

The study was completed in September 2002 and conducted at 21 sites across 15 states in the United States. The protocol and consent procedures were approved by institutional review boards, and after a complete description of the study was given to the subjects, signed consent forms were obtained from patients prior to participation in the study. Almost all participants (95%) were outpatients at the time of enrollment. Patients were randomized to open-label treatment with olanzapine ($N = 229$), typical antipsychotics of physician's choice ($N = 214$), or risperidone ($N = 221$). Subjects could, if clinically warranted, be switched from the initial randomized antipsychotic drug after a minimum of 8 weeks of therapy.

Measures

The current analysis included subjects who had PANSS scores at both Week 2 and Week 8 of the study and completed the first 8 weeks of treatment on their initially randomized antipsychotic, thus excluding patients who switched medication prior to Week 8, discontinued the study prior to Week 8, and those who did not have PANSS scores at Week 2 or 8. The analytical sample (443 or 66.7% of 664 enrollees) reflects selective attrition in which switching was responsible for about one-fourth of the attrition rate (50 of 221, or 23%). Switching was primarily due to adverse events (22 or 44%), patient request (12 or 24%), and lack of efficacy (10 or 20%). Another one-fourth of the attrition rate was due to patients discontinuing the study (54 of 221 or 24%) for various reasons, primarily due to patient decision (21 of 54 or 39%), lost to follow-up (12 of 54 or 22%), and physician decision (11 of 54 or 20%). The rest of the attrition (117 of 221 or 53%) was due to missing PANSS scores at Week 2 or 8. Per protocol, patients continued in the study even if missed assessments.

Subjects were defined as “early responders” if they experienced at least 20% improvement (decrease) on the PANSS total score from baseline (“minimal improvement”)¹⁸ at 2 weeks of treatment, and “early nonresponders” were subjects who failed to achieve this level of symptom improvement at 2 weeks. At the end of 8 weeks of treatment, all subjects were classified as either “responders” or “nonresponders” based on the same criteria used at 2 weeks.

In addition to assessing the accuracy of early response/nonresponse at 2 weeks as a predictor of subsequent response/nonresponse to treatment at 8 weeks, the early responders were compared with early nonresponders on symptom remission, levels of functioning, patients'

perceptions of medication influence, and total direct health care costs. The definition of symptom remission was based on the Schizophrenia Working Group expert consensus criteria,¹⁹ which define remission as a score of mild or better (3 or less) on 8 PANSS items: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), unusual thought content (G9), mannerisms and posturing (G5), blunted affect (N1), passive/apathetic social withdrawal (N4), and lack of spontaneity and flow of conversation (N6). Although this definition also requires maintaining mild symptom severity level for at least 6 months (severity and duration criteria), we used only the severity criterion because the current analysis was limited to the first 8 weeks of treatment. Levels of functioning were assessed with the Medical Outcome Survey-Short Form 36 (SF-36),²⁰ a patient-rated scale assessing physical and mental health functioning on 8 subscales and also providing 2 composite scores—for mental health and for physical health functioning. Patients' attitudes and behavioral factors influencing their adherence with antipsychotic medication were assessed with the Rating of Medication Influences (ROMI).²¹ The scale includes 9 items depicting reasons for medication adherence and 10 items with reasons for nonadherence, each rated on a 3-point scale from none (1) to strong (3). ROMI items were found to represent 5 underlying factors: negative aspects of medication, denial of illness, positive external influence, perceived medication benefit, and stigma.²² In addition, the "perceived medication benefit" factor was found to be the only strong predictor of treatment duration among the 5 underlying dimensions of medication influence. Higher levels of perceived beneficial effect of medication were associated with reduced risk of early treatment discontinuation, and patients with greater beliefs in the beneficial effect of their medication had greater symptom improvements and were more satisfied with their quality of life.²²

Because the parent study¹⁵ was a cost-effectiveness study, it included systematic abstraction of resource utilization from patients' medical records, which provided data for calculating total direct health care costs for each patient. The economic analysis was conducted from the perspective of the public payer health care system, thus including only direct medical costs. Included were costs of treatment resources considered to be "mental health" (eg, antipsychotic and other psychotropic medications, psychiatric hospitalizations, outpatient visits to psychiatrists, etc) as well as those considered to be "nonpsychiatric" resources (eg, nonpsychotropic medications, hospitalizations for physical illnesses, primary care physician visits, nonprotocol laboratories). With information from patient report, medical records, and administrative databases, site personnel completed the resource utilization forms. Units of specific service use for individual patients were documented and coded (but not assigned costs) at each study site. Medicare pub-

lic data (based on 2001 national average charge and payment schedules) were used as a costing benchmark. A summary of unit costing sources for each resource component can be found in a previous publication.¹⁵ These cost data were used to calculate the cost for the first 8 weeks of treatment for each patient.

Statistical Analysis

Rates of early response and early nonresponse were calculated for all patients at 2 weeks and 8 weeks of treatment. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall predictive accuracy were calculated based on early response/early nonresponse at 2 weeks and subsequent response/nonresponse at 8 weeks. Sensitivity was defined as the conditional probability that a responder is correctly identified, ie, the proportion of 8-week responders correctly identified at 2 weeks. Specificity was defined as the conditional probability that a nonresponder is correctly identified, ie, the proportion of 8-week nonresponders correctly identified at 2 weeks. PPV provided confidence in predicted positive values, defined as the proportion of patients who were responders at 8 weeks among those classified as responders at 2 weeks. NPV provided confidence in predicted negative values, defined as the proportion of patients who were nonresponders at 8 weeks among those classified as nonresponders at 2 weeks. (NPV is of greater practical interest because nonresponders are targeted for medication change.) Predictive accuracy—an overall measure of performance of the response marker—was defined as the proportion of patients whose 2-week status (early response or nonearly response) accurately predicted their 8-week status.

To assess robustness of the findings, we conducted a sensitivity analysis in which the analysis was repeated using an absolute (rather than a relative) definition of early response/early nonresponse⁹: mild or better score (3 or less) on all 4 PANSS psychotic items (unusual thought content, suspiciousness, hallucinations, and conceptual disorganization).

In addition, the 2 patient groups (early responders and early nonresponders) were compared on change from baseline to 8 weeks of treatment on rates of symptom remission, levels of functioning (per SF-36), and total direct health care costs. Patients' perceptions of medication influence on adherence were compared using the ROMI, but because this measure was not assessed at baseline, change scores from baseline were not feasible and group comparisons were conducted only for the 8-week time point.

Comparisons of early responders and early nonresponders during the first 2 weeks of treatment and on their changes from baseline to 8 weeks on symptom remission rates, level of functioning, perceptions of medication influence, and health care costs were conducted using unpaired *t* test, chi-square test, Fisher exact test, and the

Wilcoxon rank sum test. For cost comparisons, nonparametric bootstrap resampling (with 10 000 replications) was used to validate the results. A 2-sided alpha level of .05 was used for tests of significance. Covariate-adjusted comparisons were made using logistic regression and analysis of covariance. Covariates included age, gender, ethnicity, PANSS total score at baseline, illness duration, duration of hospitalization in the year prior to enrollment, current substance abuse diagnosis, and having health insurance or not. Covariates were identified a priori as those associated with differential outcomes in the treatment of schizophrenia.^{23,24} The analysis did not use assigned antipsychotic as a covariate due to the design of the study in which patients could be switched to another antipsychotic if warranted per clinician's judgment. As reported in the primary publication of the parent study,¹⁵ a significantly larger proportion of patients randomized to conventional antipsychotics and risperidone were switched to another antipsychotic compared with patients randomized to olanzapine (14% olanzapine, 31% risperidone, and 53% conventional, $P < .001$). Thus, there are potential complications with interpretation of such data—especially for analyses involving the 8-week data.²⁵

Results

Patient Baseline Characteristics

Baseline characteristics of early responders ($N = 98$, 22.1%) and early nonresponders ($N = 345$, 77.9%) are presented in table 1. The 2 groups did not significantly differ on any of the 29 baseline demographic or clinical characteristics with the exception of baseline PANSS total score, PANSS impulsivity/hostility, and PANSS anxiety/depression subscales on which early responders had a significantly higher baseline symptom severity score than early nonresponders. Baseline values are not available for ROMI scores because it was not assessed at baseline. Similarly, health care costs were not assessed for the period just prior to enrollment (“baseline”).

Patients who were included in these analyses did not significantly differ from excluded patients on most baseline characteristics including age, gender, race, employment, PANSS total score, past year psychiatric hospital duration, inpatient at study start, duration of psychiatric diagnosis, age at onset of diagnosis, and health insurance. However, the excluded patients were significantly more likely to be married (24% vs 15%, $P = .002$) and had a significantly higher mean (SD) number of prior episodes [7.6 (11.2) vs 6.6 (9.1), $P = .041$].

Predicting Subsequent Response

Early response or nonresponse—following 2 weeks of treatment—was found to accurately predict subsequent response or nonresponse at 8 weeks because most

(71.8%) of the eventual responders and nonresponders after 8 weeks of treatment with a typical or an atypical antipsychotic were correctly identified after 2 weeks of treatment with the same antipsychotic agent. The percentage of patients who were responders and nonresponders at both time points (2 and 8 weeks) was 14.9% and 56.7%, respectively. The overall accuracy level (71.8%) reflects the combination of these 2 groups. Specificity level was high (88.7%), indicating a high probability that nonresponders are correctly identified, accompanied by moderate sensitivity (41.5%, probability that responders are correctly identified), moderate PPV (67.4%), and high NPV (73.0%).

A sensitivity analysis, which employed an absolute definition of response (mild or better score on 4 PANSS psychotic items), replicated the findings. Using this secondary response definition, patients were identified as early responders ($N = 167$, 37.7%) or nonresponders ($N = 276$, 62.3%), and most (75.6%) of the eventual responders or nonresponders after 8 weeks of treatment with a typical or an atypical antipsychotic were correctly identified after 2 weeks of treatment with the same agent. Level of specificity was high (83.9%), with moderate sensitivity (65.1%), high PPV (76.1%), and high NPV (75.4%).

Sensitivity Analyses

In order to assess whether low baseline severity in a subgroup of patients may confound the results and diminish the power to show a signal (because about 10% were remitted at baseline), we repeated the analyses on a subgroup of patients who were at least moderately ill at baseline ($N = 219$). We defined “at least moderately ill” as having a baseline PANSS total score 75 or more¹⁸ and at least a moderate level (score ≥ 4) on at least 2 of 4 psychotic items on the PANSS (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content). Results were highly consistent with the original analysis. The overall predictive accuracy was essentially unchanged (slight decline from the original 71.8% to 70.8%), and the proportion of patients deemed early responders slightly increased (from 22.1% to 25.1%). There was some improvement in sensitivity (from 41.5% to 45.4%), specificity (from 88.7% to 91.0%), and PPV (from 67.4% to 80%), with decline in NPV (from 73.0% to 67.7%).

To further assess the robustness of the findings, analyses were repeated using assigned treatment (olanzapine, risperidone, conventional antipsychotics) as an additional covariate. Results were unchanged.

Symptom Remission

Compared with early responders, early nonresponders were less likely to achieve symptom remission (severity criterion) following 8 weeks of treatment. Although early responders and early nonresponders did not significantly

Table 1. Comparison of Early Responders and Nonresponders on Baseline Demographic and Clinical Characteristics

Variable	Responders at 2 wk, <i>N</i> = 98	Nonresponders at 2 wk, <i>N</i> = 345	<i>P</i> Value
Mean age (SD)	44.0 (14.2)	43.5 (11.3)	.975
Gender: % male	58.2	62.9	.505
Race			.335
Caucasian	52 (53%)	200 (58%)	
African American	37 (38%)	105 (30%)	
Other	9 (9%)	40 (12%)	
Married	16 (16%)	52 (15%)	.988
Currently employed	17 (17%)	63 (18%)	.972
Mean prior episodes	6.2 (6.7)	6.7 (9.7)	.959
Past year psychiatric hospital duration			.826
None	71 (72%)	243 (72%)	
<1 mo	19 (19%)	57 (17%)	
1 mo plus	8 (8%)	38 (11%)	
Mean PANSS total score, mean (SD)	89.8 (21.6)	84.4 (20.1)	.023
PANSS positive subscale mean (SD)	22.5 (6.5)	21.6 (6.2)	.201
PANSS negative subscale mean (SD)	221 (6.5)	209 (7.2)	.131
PANSS disorganized thoughts subscale mean (SD)	21.9 (6.5)	21.0 (6.2)	.225
PANSS impulsivity/hostility subscale mean (SD)	9.7 (3.8)	8.6 (3.6)	.004
PANSS anxiety/depression subscale mean (SD)	13.6 (4.5)	12.3 (4.1)	.010
Remitted ^a at baseline, <i>n</i> (%)	11 (11%)	33 (10%)	.244
Inpatient during randomization	2 (2%)	18 (5%)	.312
Duration of psychiatric diagnosis (y)	21.4 (13.9)	21.3 (11.7)	.959
Age at onset of diagnosis	22.6 (9.7)	22.1 (9.1)	.959
Assigned treatment <i>n</i> (%)			.886
Olanzapine	36 (37)	129 (37)	
Risperidone	34 (35)	105 (30)	
Conventional antipsychotics	28 (28)	111 (32)	
SF-36 ^b bodily pain	-0.32	-0.32	.858
SF-36 ^b general health	-0.48	-0.61	.225
SF-36 ^b mental health	-0.95	-0.88	.891
SF-36 ^b physical functioning	-0.72	-0.72	.546
SF-36 ^b role—emotional	-0.81	-0.94	.484
SF-36 ^b role—Physical	-0.56	-0.81	.059
SF-36 ^b social functioning	-0.89	-1.00	.243
SF-36 ^b vitality	-0.63	-0.55	.721
SF-36 ^b physical health component score	-0.34	-0.48	.109
SF-36 ^b mental health component score	-0.95	-0.92	.976
Health insurance			.363
Medicaid	37 (38%)	130 (40%)	
Medicare	28 (29%)	93 (28%)	
Private insurance	19 (20%)	37 (11%)	
Other insurance	0 (0%)	17 (5%)	
Uninsured	13 (13%)	52 (16%)	

Note: PANSS, Positive and Negative Syndrome Scale; SF-36, Medical Outcome Survey-Short Form 36.

^aRemitted (severity criteria) defined as mild or better scores (≤ 3) on 8 PANSS items (P1, P2, P3, N1, N4, N6, G5, G9).¹⁸

^bStandardized SF-36 score relative to general population norms.

Table 2. Comparisons of Early Responders and Early Nonresponders on Change in SF-36 Subscale and Composite Scores from Baseline to 8 Weeks

Variable	Responders at 2 wk, N = 98, Mean (SD)	Nonresponders at 2 wk, N = 345, Mean (SD)	P Value
Changes in SF-36			
Mental health	+0.37 (1.20)	+0.08 (1.09)	.014
General health	+0.09 (1.01)	+0.08 (0.95)	.228
Role/emotional	+0.39 (1.55)	+0.23 (1.44)	.020
Role/physical	+0.18 (1.30)	+0.17 (1.25)	.218
Social functioning	+0.45 (1.41)	+0.24 (1.22)	.035
Bodily pain	+0.29 (1.21)	+0.18 (1.19)	.426
Physical functioning	+0.19 (1.34)	+0.01 (1.08)	.049
Vitality	+0.40 (1.13)	+0.17 (0.97)	.033
Mental health composite score	+0.49 (1.30)	+0.20 (1.10)	.005
Physical health composite score	+0.08 (1.02)	+0.09 (0.88)	.495

Note: SF-36, Medical Outcome Survey-Short Form 36.

differ on symptom remission rates at baseline (11.2% vs 9.6%, $P = .702$), the change in symptom remission rate from baseline to 8 weeks was significantly larger for early responders ($P < .001$) because 46.9% of the early responders and only 27.5% of the early nonresponders were in remission following 8 weeks of treatment ($P < .001$). The increase in remission rate from baseline to 8 weeks for early responders (35.7%) was nearly twice as high as that for early nonresponders (18.0%).

Level of Functioning

Changes on SF-36 scale scores for the 2 groups from baseline to 8 weeks of treatment are presented in table 2. Although the groups did not significantly differ on any mean scale score at baseline, following 8 weeks of treatment with the same antipsychotics, the early nonresponders had significantly lower levels of improvement on the mental health composite score and on 5 of 8 functional domains: mental health, role emotional, social functioning, physical functioning, and vitality. More specifically, the early responders, but not the early nonresponders, improved by about one-half a SD (+0.49, change from -0.95 to -0.46) on the mental health component score and on social functioning (+0.45, change from -0.89 to -0.44), suggesting some clinically meaningful changes in early responder’s level of functioning in these domains. The 2 groups did not significantly differ on changes in the physical health composite score or on 3 physical health–related scales: general health, role physical, and bodily pain.

Perceptions of Medication Influence

Scores on the ROMI for the 2 groups on the 5 dimensions of medication influence at 8 weeks are presented in

Table 3. Comparisons of Early Responders and Early Nonresponders on Perceptions of Medication Benefits and Estimated Health Care Costs Following 8 Weeks of Treatment

Variable	Responders at 2 wk, N = 98, Mean (SD)	Nonresponders at 2 wk, N = 345, Mean (SD)	P Value
ROMI factor scores			
Negative aspects of medication	1.51 (0.64)	1.50 (0.61)	.952
Denial of illness	1.25 (0.47)	1.33 (0.57)	.174
Positive external influence	2.05 (0.71)	1.95 (0.72)	.360
Perceived medication benefit score	2.52 (0.49)	2.32 (0.57)	.004
Stigma	1.21 (0.38)	1.27 (0.52)	.156
Estimated health care costs			
Medication costs	\$569 (435)	\$623 (479)	.276
Nonmedication costs	\$1533 (3846)	\$3726 (7697)	.011
Total health care costs	\$2102 (3866)	\$4349 (7809)	.010

Note: ROMI, Rating of Medication Influences.

table 3. Compared with early responders, early nonresponders had significantly ($P = .004$) lower (worse) scores following 8 weeks of treatment only on the perceived medication benefits dimension, which is comprised of 4 items: perceived daily benefits, fear of relapse, side effect relief, and fulfillment of life goals.

Health Care Costs

Differences between the groups on direct total health care costs and medication and nonmedication costs following 8 weeks of treatment are presented in table 3. The total direct health care cost was almost twice as high for early nonresponders as for early responders (\$4349 vs \$2102, $P = .010$). This group difference was primarily driven by nonmedication costs, which were significantly higher for early nonresponders (\$3726 vs \$1533, $P < .011$), while the groups did not significantly differ on medication costs. Significant group differences in direct health care costs were evident following only 2 weeks of treatment, and costs for early nonresponders also remained higher for Weeks 3 through 8. After 2 weeks, early nonresponders accrued twice as high total health care costs compared with the early responders (\$1194 [SD = \$1119] vs \$581 [SD = \$2235], $P = .021$), driven also by significantly higher direct nonmedication costs (\$1042 [SD = \$2213] vs \$451 [SD = \$1119], $P = .025$), without significant differences in medication costs (\$152 [SD = \$125] vs \$130 [SD = \$83], $P > .05$).

Discussion

Although this study's core finding—that early nonresponse predicts later nonresponse—is well established, this replication study extends prior research in 3 important ways. First, this study includes mostly outpatients and uses less strict entry criteria than those used in double-blind, controlled RCTs, thereby increasing the generalizability of the findings to settings and patients often excluded from the currently published studies on this topic. Second, this study also uses an absolute response criterion (ie, no more than mild severity on all 4 PANSS psychotic subscore items) to overcome the fact that relative response criteria are vulnerable to the effect of baseline scores and may either under- or overestimate the effect of the antipsychotic. And lastly, this study assesses—for the first time—the ramifications of early response/nonresponse to treatment, by assessing clinical and functional outcomes, subjective patient perceptions, and health care cost.

This study helps advance the importance of early evaluation of patients' response to antipsychotics for potential change in regimen from the patient, clinician, family member, and payer perspectives. It shows that continued exposure to initial treatment, despite less than minimal symptom improvement at 2 weeks, not only prolongs suboptimal treatment unnecessarily but is also associated with more negative subjective perceptions of medication's benefits, with poorer functional outcomes, and with higher health care costs.

Consistent with prior schizophrenia studies that used data from RCTs with predominately inpatients,^{8–11} the current study of antipsychotic therapy in the usual care of predominately outpatients with schizophrenia also revealed that early nonresponse to treatment is a robust and accurate predictor of subsequent nonresponse to continued therapy with the same medication. The current study further expands on prior research by showing that patients who do not experience early response (early nonresponders following 2 weeks of treatment) demonstrate significant and clinically meaningful poorer outcomes in symptomatic, functional, and economic terms when their treatment is continued with the same antipsychotic medication for an additional 6 weeks. The validation of previous research may enhance the generalization of the findings to patients with schizophrenia treated in outpatient practice settings and underscores the implications of this clinical marker to usual care where timely identification of early nonresponders may help minimize prolonged exposure to suboptimal or ineffective treatment strategies.

This study found that schizophrenia patients with less than minimal improvement in their symptomatology following 2 weeks of antipsychotic therapy are unlikely to show at least a minimal improvement at 8 weeks of treatment if treatment continued with the same medication.

Furthermore, the current study found a high level of specificity (89%) and NPV of 73%, which were maintained when the definition of early response was altered from a relative response (20% reduction in PANSS total score from baseline) to an absolute response (mild or better on 4 core psychotic symptoms). Although clinicians are more likely to monitor patients' treatment progress using 4 psychotic items than administer the 30-item PANSS, it is notable that a 20% reduction in PANSS total score from baseline to 2 weeks of treatment (“minimal improvement”) was previously found to be comparable to a 1-point improvement on the Clinical Global Impressions-Improvement,¹⁸ a simpler measure widely used by clinicians. Furthermore, from a clinical perspective, demonstrating high specificity and NPV is most important because clinicians typically focus on the nonresponding patients who require “rescue” strategies in the form of changes in current treatment regimens. Although current findings are reported for a heterogeneous group of outpatients in terms of illness severity, sensitivity analyses replicated the findings in a subgroup of patients who were at least moderately ill at baseline.

It is important to note that although early nonresponse appears to be a robust predictor of subsequent nonresponse to initiated medication, some early nonresponders will become subsequent responders following 8 weeks of treatment (about 27% “false negatives”). Future research is needed to help identify reliable predictors of delayed response among these “false negatives” to enhance the accuracy of this treatment response marker. In addition, current findings do not necessarily imply that an early switch to another antipsychotic will increase likelihood of eventual response. This is an empirical question that will require a study in which early nonresponders are randomly assigned to double-blind therapy with either a different “rescue” treatment option or continue on the same initial medication.

Current findings highlight the importance of timely identification of early nonresponders for potential change in medication regimen and the impact on outcomes it could have on the patient, the clinician, the family member, and the payer. Early nonresponding patients are less likely to achieve subsequent symptom remission, to function at a poorer level within multiple domains including greater deficits in social relationships and vitality, to incur total direct costs that are twice as high as early responders (driven by high nonmedication costs), and to perceive medications as less beneficial to them.

It is important to note that despite statistically significantly greater functional improvements among early responders compared with early nonresponders, both groups were still functioning at a poorer level—at least one-half SD—below the general population norms following 8 weeks of treatment. However, the early responders (but not the early nonresponders) experienced after 8 weeks of treatment a level of functional improvement equivalent to about one-half a SD, a magnitude that is

often considered a minimally important difference on health-related quality-of-life instruments for patients with chronic diseases.²⁶ For example, the baseline mental health and social functioning levels were poorer than the general population for both early responders and early nonresponders—about 1 SD below the norm. However, following 8 weeks of treatment, early responders improved by about one-half a SD on the mental health component score and on social functioning, suggesting some clinically meaningful changes in early responder's level of functioning in these important domains. Further study is needed, however, to translate the clinical meaningfulness of gaining one-half SD on SF-36 scores in the treatment of schizophrenia, especially how such changes may impact patients' life satisfaction, occupational functioning, housing arrangements, and other important aspects of daily life.

In addition, the finding that early nonresponders appear to perceive medications as less beneficial to them is of clinical importance because the likelihood of becoming medication nonadherent was previously found (results are drawn from the same study from which this subsample was drawn) to be greater among schizophrenia patients who believed medications were of low benefit.²⁷ Moreover, a recent study²² showed that a lower level of perceived beneficial effects of medication is associated with a higher rate of early treatment discontinuation. Because better adherence is linked to favorable long-term outcomes,²⁸ including reduced risk of relapse and hospitalization, the current findings suggest that identification of early nonresponders may be valuable in the clinical and economic realms for the patients and other health care decision makers.

The present study has, however, some important limitations. First, this was a post hoc analysis limited to patients who completed 8 weeks of treatment. There is a need for additional studies that assess a priori, the predictive accuracy of early nonresponse as a reliable marker of eventual nonresponse among patients treated with specific antipsychotics. Second, this study examined predictive accuracy using conditional probabilities, although the use of other methods, such as receiver-operator curves, may provide additional useful information particularly on the impact of using different initial and subsequent levels of response at different time points. This could not be readily done in this analysis due to constraints of the study design (patients could and did switch to other antipsychotics, if clinically warranted, following 8 weeks of treatment). Another important issue is that early response does not necessarily mean marked improvement or remission. To fully consolidate the gains of a successful antipsychotic therapy will require longer treatment duration as most patients may take 8–12 weeks to reach stable symptom improvements.^{29,30} Thus, although response at 2 weeks appears to reliably predict subsequent outcome, we are not in any way suggesting

that patients are remitted or much improved by 2 weeks if they respond to their medication.

In conclusion, utilizing data from a naturalistic study of antipsychotics in the treatment of predominately outpatients with schizophrenia, early nonresponse to treatment was found to accurately predict subsequent nonresponse to continued treatment with the same antipsychotic agent after 8 weeks. Furthermore, early nonresponders demonstrated poorer clinical, functional, and economic outcomes following 8 weeks of treatment. Current findings suggest that identifying early nonresponders is an important step in effective management of persons with schizophrenia, a practice that may lead to tailored therapeutics and help minimize exposure to suboptimal or ineffective treatment strategies.

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