Prognostic Subgroups for Remission, Response, and Treatment Continuation in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Trial

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ABSTRACT

Objective: Identify moderators of treatment outcome from antipsychotic pharmacotherapy in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial. Specifically, we used logistic regression and receiver operating characteristic (ROC) analysis to explore the association between baseline characteristics and treatment outcomes in the CATIE trial.

Method: This is a secondary analysis of the CATIE trial in which 1,460 adults with a *DSM-IV* diagnosis of schizophrenia were randomly assigned to olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone treatment for up to 18 months or until discontinuation between January 2001 and December 2004. Logistic regression was used to examine baseline characteristics associated with remission, response, and treatment continuation at 3 and 6 months of treatment. ROC analyses identified subgroups associated with similar likelihood of treatment outcome. Remission was defined by scores of selected items on psychoticism, disorganization, and negative symptoms. Response was defined as a 50% or greater improvement on the Positive and Negative Syndrome Scale.

Results: The most consistent predictors of poor outcome on all variables were low scores on neurocognitive tests (in particular verbal memory) (OR = 1.13–1.49, $P < .05$); previous reported side effects (OR = 0.49–0.69, $P < .05$); negative attitude to medication (OR = 1.03–1.10, $P < .05$); comorbid depression (OR = 0.47–0.51, $P < .05$); psychosocial factors such as unemployment (OR = 0.74–0.75, $P < .05$), homelessness (OR = 0.54, $P < .05$), and living alone (OR = 1.58–1.94, $P < .01$); and random assignment to a medication other than olanzapine (OR = 1.54–2.04, $P < .01$). ROC analysis demonstrated prognostic subgroups with large differences in response likelihood.

Conclusions: Baseline characteristics in schizophrenia are informative regarding clinically important treatment outcomes with respect to antipsychotic pharmacotherapy. Further research should examine whether interventions that target improvement of patients' deficits in neuropsychological function and attitude toward medication as well as decreasing patients' social isolation can improve treatment outcomes with antipsychotic treatment in schizophrenia.

Trial Registration: ClinicalTrials.gov identifier: NCT00014001

J Clin Psychiatry 2015;76(11):1535–1545
dx.doi.org/10.4088/JCP.14m09320

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Schizophrenia is ranked by the World Health Organization as the third most debilitating condition.[1] Antipsychotic medications are the first-line treatment for schizophrenia.[2] Although these medications demonstrate efficacy for positive symptoms, many patients with schizophrenia continue to have debilitating negative symptoms, cognitive deficits, and side effects.[3] In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, only 18.9% of participants responded to antipsychotic medication,[4] and 74% of participants discontinued medication by 18 months.[5]

Given that (1) a large fraction of patients do not attain remission or response with antipsychotic treatment, (2) antipsychotics take several weeks to achieve maximal efficacy, and (3) antipsychotics have significant side effects that limit safety and tolerability, identifying moderators of efficacy of antipsychotic treatment is important for improving treatment outcomes for individuals with schizophrenia. Identifying subgroups of patients with differential likelihoods of treatment outcomes (either positive or negative) will help individualize care.

We used traditional logistic regression techniques as well as receiver operating characteristic (ROC) analysis to examine the first treatment phase of the CATIE trial, which enrolled 1,460 patients with schizophrenia and treated them for 18 months with perphenazine or 1 of 4 atypical antipsychotic agents in "real world" settings.[5,6] Both statistical approaches were used to identify baseline demographic, social, and clinical characteristics associated with clinically salient outcomes after 3 and 6 months of treatment. Prognostic information provided by our analysis can help guide treatment decisions early on in the pharmacotherapy of schizophrenia.

METHOD

Study Overview

The rationale, design, and methods of the CATIE study have been described elsewhere.[5,6] We specifically utilized data from phase 1 of the CATIE trial, which was a large, double-blind clinical trial funded by the National Institute of Mental Health (NIMH) in which 1,460 subjects were treated with olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone for up to 18 months or until discontinuation. The trial was registered on ClinicalTrials.gov (identifier: NCT00014001).

Subjects

Subjects were recruited from 16 university clinics, 10 state mental health agencies, 7 Veterans Affairs medical centers, 6 private nonprofit agencies, 4 private-practice sites, and 14 mixed-system sites within the United States. The research protocol was approved by the institutional review boards at all sites, and all subjects provided informed consent.

To be included in the CATIE trial, outpatients needed to be adults aged 18–65 years with a diagnosis of schizophrenia based on *DSM-IV* who were able to take oral antipsychotics. Patients were excluded from the CATIE trial if they had any of the following: a diagnosis of schizoaffective disorder, mental retardation, or other cognitive disorders; a history of serious adverse reactions to the proposed treatments; an occurrence of only 1 schizophrenic episode; a history of treatment resistance, defined by the persistence of severe symptoms despite adequate trials of 1 of the proposed treatments or prior treatment with clozapine; a serious and unstable medical condition; or pregnancy or breastfeeding status.

Assessment

At baseline, information was obtained on a range of demographic and clinical characteristics including physiologic and neuropsychological measures. The primary outcome measures were the medication continuation rate and the Positive and Negative Syndrome Scale (PANSS),[7] which was used to assess efficacy. The PANSS was assessed at 1, 3, 6, 9, 12, 15, and 18 months. Patients were treated between January 2001 and December 2004. The definitions for remission and response were adapted from previous research.[8] A patient was considered remitted if his or her score on all of 8 specific items of the PANSS was mild or better (3 items on psychoticism, 2 on disorganization, and 3 on negative symptoms); in contrast to previous definitions, a time criterion was not included in our remission criteria given the scarcity of ratings in the trial. Response was defined as a 50% or greater improvement on the PANSS. Continuation of treatment was also included as a primary outcome. We examined all outcome variables at 3 and 6 months of treatment to identify predictors in the earlier phases of treatment.

Intervention

Participants were randomly assigned to receive flexibly dosed olanzapine (7.5–30 mg daily), quetiapine (200–800 mg daily), risperidone (1.5–6 mg daily), perphenazine (8–32 mg daily), or ziprasidone (40–160 mg daily) in a double-blinded fashion. Participants who had tardive dyskinesia at baseline were not assigned to perphenazine.

Statistical Analysis

Data preparation was conducted using SAS version 9.2 (SAS Institute) and Microsoft Excel (Microsoft Corp). Both logistic regression models and signal detection methodology were used to find the best prediction model. SAS was used for simple and multiple logistic regression models. The ROC analysis was performed using free software available online (http://www.stanford.edu/~yesavage/ROC.html). Data utilized in this study were obtained from the NIMH-supported CATIE public access database.

Logistic regression models assessed the association of demographic, social, and clinical characteristics with remission and response at 3 and 6 months. Predictor variables entered in the simple logistic regression are listed in Table 1.[9–27]

All predictor variables were tested for main effects and interaction with treatment assignment. Significant predictors ($P < .05$) from the simple regression models were entered into a backward stepwise multiple logistic regression model to assess the unique and independent contribution of these variables to remission and response rates.

ROC analysis was used as an alternative prediction model. ROC analysis is a nonparametric method that operates via recursive partitioning. It aims at identifying subgroups of individuals who have a higher or lower probability of achieving a particular binary outcome.[28] Remission, response, and treatment continuation by the end of 3 months (as well as 6 months) were utilized as the binary outcomes for ROC analysis. The a priori stopping rules for ROC analysis were (1) a maximum amount of 8 subgroups, (2) a subgroup size of less than 20, and (3) *P* value for group difference greater than or equal to .05. After the last step of the ROC analysis was reached, we calculated the probability of treatment success (remission, response, or continuing treatment) and presented results as hierarchical decision tree diagrams. The model was calculated using the same predictors as previous regression models.

Clinical Points

- The best predictors of poor treatment outcome in schizophrenia are low scores on neurocognitive tests, negative attitude toward medication, comorbid depression, previously reported side effects, and low socioeconomic status.
- The best predictor for good treatment outcome was assignment to olanzapine.
- This study suggests the possibility that treatment outcomes in schizophrenia may be improved not only by using novel pharmacologic interventions but also by targeting interventions to (1) improve or help compensate for deficits in neuropsychological function, (2) direct patient attitudes toward medication, and (3) improve patients' social environment.

RESULTS

Subjects

Demographic, clinical, and neurocognitive characteristics for the subjects were published previously.[5,29] The initial sample size was 1,460. Depending on the availability of treatment outcome at 3 months and treatment group, the actual sample sizes varied between 958 for 3-month outcomes and 889 for 6-month outcomes. Treatment response was the rarest outcome, with 12.4% of subjects meeting response criteria at 3 months (15.5% at 6 months),

Table 1. Predictor Variables in Simple Logistic Regression and Receiver Operating Characteristic Analyses[a]

Predictor Variables		
Domain	Variable	Variable Coding
Demographic measures	Age	Years
	Race: Black	Yes/no
	Race: White	Yes/no
	Ethnicity	Hispanic/non-Hispanic
	Gender	1 = male, 2 = female
Socioeconomic variables	Married	Yes/no
	Education level (patient)	0 (no high school)–8 (advanced degree)
	Education level (parent)	0 (no high school)–8 (advanced degree)
	Employment status	1 (full-time), 2 (half-time), 3 (unemployed)
Quality of life		
Quality of Life Scale	Living alone	Yes/no
	Being homeless	Yes/no
	Having close friends	Yes/no
	Receiving help from family members or friends	Yes/no
	Being reminded to take or given medication	Yes/no
Quality of Life Interview	Feeling about life in general	1 (terrible)–7 (delighted)
Health		
12-Item Short-Form Health Survey	Mental health mean score (baseline and phase 1)	US general population norm: average = 50 and SD = 10. Higher scores reflect better health
	Physical health mean score (baseline and phase 1)	
Family-reported daily function	Frequency that mental health appointments were made	1 (never)–4 (always)
	Health insurance payments	Yes/no
	Excessive alcohol use	Yes/no
Clinical predictors		
Current and lifetime Axis I comorbidities rated with Structured Clinical Interview for *DSM-IV* Axis I Disorders	Major depressive disorder, alcohol abuse and dependence, substance abuse and dependence, obsessive-compulsive disorder, posttraumatic stress disorder, panic disorder, agoraphobia, social phobia, specific phobia, other anxiety disorders	Yes/no
Other clinical measures	Calgary Depression Scale	Total score (9–36) and suicidal ideation item: 1 (absent)–4 (severe)
	Radioimmunoassay of hair specimens for illicit substances: cocaine, opiates, phencyclidine, methamphetamine, tetrahydrocannabinol	Yes/no
	Number of general medical diagnoses	
Previous adverse events	Akathisia, akinesia, constipation, gynecomastia, incontinence, insomnia, sialorrhea, sleepiness, menstrual, faintness, dry mouth, sexual, rash, urinary, weight gain	Yes/no
	Suicide attempts or self-injury in the past 6 months	Yes/no
Neuropsychological measures	Verbal memory: Hopkins Verbal Learning Test	*z* Score
	Vigilance: Continuous Performance Test; computerized test of visuospatial working memory	*z* Score
	Processing speed: compound *z* score of Controlled Oral Word Association Test, categorical instances; Grooved Pegboard; and Wechsler Adult Intelligence Scale-Revised–Digit Symbol Test	*z* Score
	Reasoning: compound *z* score of Wisconsin Card Sorting Test-64 Card Computerized Version and Wechsler Intelligence Scale for Children, Third Edition, mazes subtest	*z* Score
	Working memory: Letter-Number Sequencing Test	*z* Score
	Neurocognitive composite *z* score of all tests above	*z* Score
Psychological variables	Insight and Treatment Attitudes Questionnaire	Total score: 0 (no insight)–22 (full insight)
	Drug Attitude Inventory	Total score: 0 (bad attitude)–10 (good attitude)
Previous treatment variables	Age when first behavioral treatment	Years
	Age when first received antipsychotic treatment	Years
	Time since first antipsychotic prescribed	Years
	Number of hospitalizations (past year, lifetime)	
	Previous adverse events to medication use	Yes/no
	Previous tardive dyskinesia	Yes/no
	Abnormal Involuntary Movement Scale	Total score: 0 (none)–28 (severe)
	Barnes Akathisia Scale	Total score: 0 (absent)–9 (severe)
	Simpson-Angus Scale	Mean score: 0 (absent)–4 (severe)
Treatment assignment		
Study medication	Olanzapine, risperidone, ziprasidone, quetiapine, perphenazine	Yes/no
Clinical site	Managed care, private, nonprofit, private practice, research only, state mental health, university clinic, Veterans Affairs	Yes/no
	Switching from antipsychotic taken at baseline (vs staying on it)	Yes/no

[a]Reference list for scales in this table: Quality of Life Scale[9]; Quality of Life Interview[10]; 12-Item Short-Form Health Survey[11]; Structured Clinical Interview for *DSM-IV* Axis I Disorders[12]; Calgary Depression Scale[13,14]; Hopkins Verbal Learning Test[15]; Continuous Performance Test[16]; Controlled Oral Word Association Test, categorical instances[17]; Grooved Pegboard[18]; Wechsler Adult Intelligence Scale-Revised–Digit Symbol Test[19]; Wisconsin Card Sorting Test–64-Card Computerized Version[20]; Wechsler Intelligence Scale for Children, Third Edition, mazes subtest[21]; computerized test of visuospatial working memory[22]; Letter-Number Sequencing Test[21]; Insight and Treatment Attitudes Questionnaire[23]; Drug Attitude Inventory[24]; Abnormal Involuntary Movement Scale[25]; Barnes Akathisia Scale[26]; and Simpson-Angus Scale.[27]

followed by remission, with 29.4% of subjects meeting criteria at 3 months (29.9% at 6 months). Sixty-five percent of subjects were still on their medications at 3 months (46.9% at 6 months), making medication continuation the most commonly achieved positive treatment outcome measure.

Three-Month Treatment Outcome

Predictors of treatment outcome. Table 2A displays baseline characteristics associated with remission, response, and continuation of treatment at 3 months in the CATIE trial in simple logistic regression. There were a large number of factors associated with all 3 treatment outcome measures. Random assignment to olanzapine was associated only with treatment continuation at 3 months (OR = 1.5, $P < .01$). Strong positive associations with most neuropsychological measures were found for remission (Hopkins Verbal Learning Test [HVLT], OR = 1.47, $P < .001$; Continuous Performance Test, OR = 1.28, $P < .01$; processing speed composite score, OR = 1.42, $P < .001$; reasoning composite score, OR = 1.22, $P < .01$; working memory composite score, OR = 1.38, $P < .001$; neurocognitive composite score, OR = 1.49, $P < .001$) and response (HVLT, OR = 1.42, $P < .001$; processing speed composite score, OR = 1.32, $P < .01$; reasoning composite score, OR = 1.24, $P < .05$; neurocognitive composite z score, OR = 1.34, $P < .01$), and a positive association with HVLT was found for treatment continuation (OR = 1.13, $P < .05$).

Backward stepwise multiple logistic regression models predicting treatment outcome. Table 2B displays the results of the best-fitting backward stepwise models for all 3 outcome variables. Stepwise logistic regression models were able to explain 8.0% of the variance in response (pseudo R^2), 16.0% in remission, and 7.1% in treatment continuation at 3 months of treatment.

Prognostic subgroups associated with treatment outcome. Figure 1A displays hierarchical prognostic subgroups for response at 3 months of treatment. Baseline clinical characteristics were able to identify subgroups with as low as an 8.0% likelihood of responding (processing speed composite z score < 0.9, being seen at a site other than private practice or state mental health) to as high as a 31.5% likelihood of responding (processing speed composite z score between 0.9 and 1.16). The most discriminative predictor of response was processing speed composite z score at a threshold of 0.9 (n = 958, $\chi^2_1 = 10.788$, $P < .01$). Better neuropsychological functioning at baseline was associated with an increased likelihood of response.

Figure 1B displays hierarchical prognostic subgroups for remission at 3 months of treatment. Baseline clinical characteristics were able to identify subgroups with as low as a 14.0% likelihood of remission (HVLT z score < 0.4, depressive symptoms present [Calgary Depression Scale score ≥ 4], age ≥ 25 years) to as high as a 70.0% likelihood of remission (HVLT z score ≥ 0.4, 12-Item Short-Form Health Survey [SF-12] mental health score ≥ 44.8, Insight and Treatment Attitudes Questionnaire total score ≥ 20). The most discriminative predictor of remission was HVLT z score at a threshold of 0.4 (n = 958, $\chi^2_1 = 31.489$, $P < .001$).

Figure 1C displays hierarchical prognostic subgroups for treatment continuation at 3 months of treatment. Baseline clinical characteristics were able to identify subgroups with as low as a 33.7% likelihood of continuing treatment (SF-12 mental health score < 29.9, reasoning composite z score < −0.29, ≥ 6 years since first antipsychotic) to as high as a 74.2% likelihood of continuing treatment (SF-12 mental health score ≥ 29.9, having close friends, reasoning composite z score ≥ −0.93). The most discriminative predictor of pharmacologic treatment discontinuation was SF-12 mental health score at a threshold of 29.9 (N = 1,460, $\chi^2_1 = 17.349$, $P < .001$). Individuals with comorbid MDD were at a higher likelihood to discontinue pharmacologic treatment.

Six-Month Treatment Outcomes

Predictors of treatment outcome. Table 3A displays baseline characteristics associated with remission, response, and continuation of treatment at 6 months in the CATIE trial in simple logistic regression. There were a large number of factors associated with all 3 treatment outcome measures. Random assignment to olanzapine was significantly associated with higher rates of response (OR = 2.04, $P < .001$) and treatment continuation (OR = 1.86, $P < .001$). Strong associations across all treatment outcome variables were found for most neuropsychological measures. Random assignment to quetiapine was negatively associated with treatment continuation (OR = 0.73, $P < .05$), and risperidone was negatively associated with response (OR = 0.57, $P < .05$). Strong positive associations with most neuropsychologic measures were found for remission (HVLT, OR = 1.49, $P < .001$; processing speed composite score, OR = 1.56, $P < .001$; reasoning composite score, OR = 1.19, $P < .05$; working memory composite score, OR = 1.38, $P < .001$; neurocognitive composite score, OR = 1.47, $P < .001$); a positive association with HVLT was found for response (OR = 1.28, $P < .01$); and a negative association with processing speed composite score was found for treatment continuation (OR = 0.89, $P < .05$).

Backward stepwise multiple logistic regression models predicting treatment outcome. Table 3B displays the results of the best fitting backward stepwise models for all 3 outcome variables. Stepwise logistic regression models were able to explain 6.5% of the variance in response (pseudo R^2), 18.1% in remission, and 5.4% in treatment continuation at 6 months of treatment.

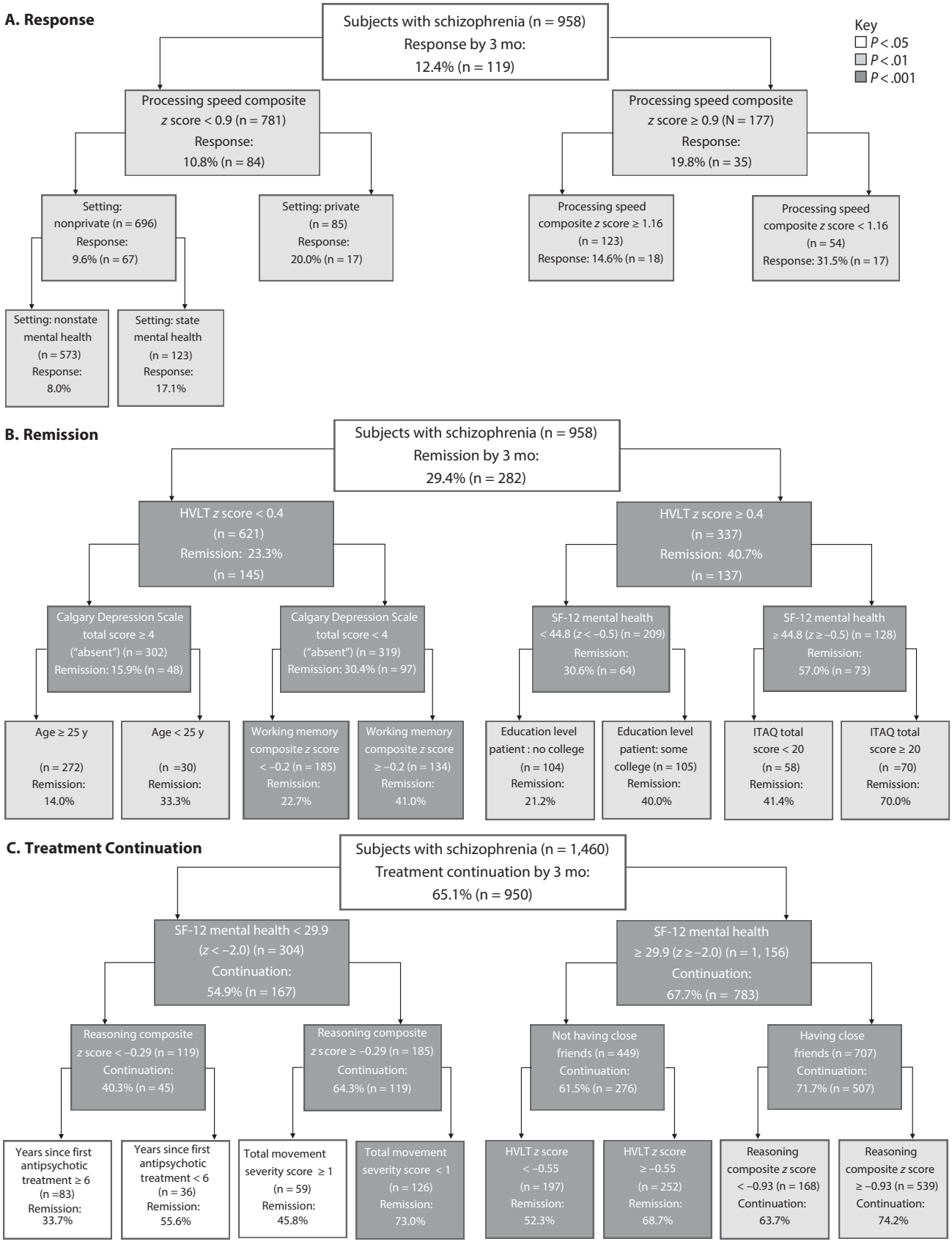
Prognostic subgroups associated with treatment outcome. Figure 2A displays hierarchical prognostic subgroups for response at 6 months of treatment. Baseline clinical characteristics were able to identify subgroups with as low as a 9.1% likelihood of responding (random assignment to a drug other than olanzapine, being seen at a site different from state mental health, HVLT z score < 1.4) to as high as a 43.4% likelihood of responding (random assignment to olanzapine, HVLT z score ≥ 0.1, neurocognitive composite z score < 0.6). The most discriminative predictor of response was random assignment to olanzapine (n = 889, $\chi^2_1 = 13.820$, $P < .001$).

Table 2. Simple and Multiple Regression Analysis Stratified by Outcome Criteria by 3 Months of Treatment[a]

	Response				Remission				Continuation			
Baseline Characteristic	OR	95% CI	Wald	*P*	OR	95% CI	Wald	*P*	OR	95% CI	Wald	*P*
A. Bivariate regression												
Categorical characteristics												
Olanzapine	1.44	0.95–2.19	2.97	.0848	0.79	0.57–1.09	2.06	.1516	**1.54**	**1.18–2.01**	**10.01**	**.0016****
Having close friends	1.45	0.96–2.20	3.04	.0814	**2.31**	**1.70–3.15**	**28.14**	**.0001*****	**1.49**	**1.19–1.85**	**12.48**	**.0004*****
Siblings help with treatment	1.31	0.74–2.33	0.88	.3489	0.80	0.50–1.26	0.93	.3338	**1.46**	**1.01–2.10**	**3.97**	**.0465***
Being homeless	1.84	0.68–5.00	1.43	.2319	1.63	0.73–3.68	1.40	.2366	**0.54**	**0.31–0.93**	**4.99**	**.0256***
Comorbid conditions												
Major depressive disorder (current)	0.66	0.30–1.46	1.07	.3005	**0.47**	**0.27–0.82**	**6.97**	**.0083****	0.71	0.48–1.05	2.87	.0900
Treatment setting												
Private, nonprofit agency	**1.94**	**1.14–3.31**	**5.96**	**.0146***	1.36	0.88–2.10	1.85	.1737	0.90	0.62–1.29	0.35	.5541
Research	0.00	0.00–1000	0.00	.9754	**0.45**	**0.21–0.98**	**4.07**	**.0436***	1.44	0.82–2.55	1.59	.2072
State mental health	1.79	1.14–2.82	6.33	**.0119***	**1.71**	**1.21–2.43**	**9.01**	**.0027****	0.82	0.62–1.07	2.09	.1485
Living alone	**1.94**	**1.30–2.91**	**10.35**	**.0013****	**1.58**	**1.16–2.14**	**8.42**	**.0037****	1.15	0.89–1.48	1.10	.2947
Side effects (previous treatment)												
Constipation	0.74	0.43–1.29	1.10	.2941	1.00	0.68–1.45	0.00	.9826	**0.60**	**0.42–0.86**	**7.85**	**.0051****
Akinesia	0.63	0.38–1.06	3.04	.0812	**0.55**	**0.38–0.80**	**9.69**	**.0019****	0.99	0.70–1.42	0.00	.9755
Insomnia	**0.49**	**0.30–0.81**	**7.72**	**.0054****	**0.66**	**0.47–0.93**	**5.78**	**.0162****	0.98	0.70–1.36	0.01	.9064
Faintness	0.95	0.59–1.60	0.03	.8589	**0.69**	**0.48–0.99**	**4.02**	**.0451***	0.94	0.65–1.30	0.13	.7171
Rash	0.47	0.19–1.21	2.45	.1173	**0.53**	**0.29–0.96**	**4.34**	**.0372***	**0.57**	**0.36–0.90**	**5.69**	**.0171***
Dry mouth	**0.62**	**0.40–0.95**	**4.80**	**.0285***	0.82	0.60–1.12	1.61	.2049	1.02	0.74–1.41	0.02	.8907
Medication at baseline												
Antidepressant treatment	0.86	0.58–1.27	0.59	.4433	0.83	0.63–1.10	1.68	.1955	**1.25***	**1.01–1.56**	4.08	.0435*
Any conventional antipsychotic	0.65	0.56–1.64	0.02	.8772	1.08	0.73–1.60	0.16	.6902	**0.68**	**0.51–0.92**	**6.20**	**.0128***
Any atypical antipsychotic	1.01	0.54–1.89	0.00	.9774	0.69	0.44–1.06	2.84	.0919	**1.49**	**1.06–2.11**	**5.14**	**.0234***
Continuous characteristics												
Age	**0.98**	**0.96–1.00**	**5.20**	**.0225***	0.99	0.98–1.00	3.00	.0834	1.01	1.00–1.01	0.84	.3605
Employment (3 = no, 1 = full-time)	1.14	0.78–1.66	0.45	.5015	**0.74**	**0.58–0.94**	**6.03**	**.0141***	0.97	0.80–1.19	0.08	.7812
Side effects (previous treatment)												
Abnormal Involuntary Movement Scale total score	0.96	0.89–1.03	1.20	.2726	**0.95**	**0.90–1.00**	**4.12**	**.0424***	**0.96**	**0.93–0.99**	**6.10**	**.0135***
Simpson-Angus Scale, mean	0.73	0.38–1.42	0.84	.3582	**0.54**	**0.33–0.88**	**6.23**	**.0126***	0.96	0.69–1.34	0.06	.8001
Calgary Depression Scale-suicidal ideation	0.83	0.53–1.30	0.67	.4145	**0.52**	**0.36–0.76**	**11.55**	**.0007*****	0.85	0.69–1.06	1.98	.1590
Calgary Depression Scale total score	0.97	0.93–1.02	1.73	.1882	**0.91**	**0.88–0.94**	**26.78**	**.0001*****	**0.97**	**0.95–0.99**	**6.26**	**.0124***
DAI total score (positive = compliant)	**1.07**	**1.01–1.13**	**5.52**	**.0188***	**1.10**	**1.05–1.14**	**18.71**	**.0001*****	**1.03**	**1.00–1.06**	**4.97**	**.0258***
Feeling about life in general	**1.32**	**1.14–1.53**	**13.94**	**.0002*****	**1.23**	**1.11–1.36**	**15.67**	**.0001*****	1.06	0.98–1.15	2.31	.1288
Insight and Treatment Attitudes Questionnaire	**1.06**	**1.01–1.11**	**5.81**	**.0159***	1.03	1.00–1.06	3.12	.0771	1.02	1.00–1.04	3.78	.0518
SF-12 mental health	1.01	0.99–1.03	2.17	.2474	**1.03**	**1.02–1.05**	**2.03**	**.0001*****	1.01	1.00–1.02	1.21	.2706
Neuropsychological measures												
Hopkins Verbal Learning Test	**1.42**	**1.16–1.73**	**11.87**	**.0006*****	**1.47**	**1.27–1.71**	**26.93**	**.0001*****	**1.13**	**1.01–1.27**	**4.29**	**.0384***
Continuous Performance Test	1.12	0.91–1.37	11.87	.2787	**1.28**	**1.10–1.49**	**10.56**	**.0012****	0.96	0.86–1.09	0.39	.5338
Processing speed composite score	1.32	1.08–1.60	7.47	.0063**	**1.42**	**1.23–1.64**	**22.29**	**.0001*****	0.98	0.87–1.09	0.17	.6825
Reasoning composite score	**1.24**	**1.01–1.52**	**4.09**	**.0433***	**1.22**	**1.05–1.41**	**6.87**	**.0088****	1.10	0.99–1.24	2.93	.0872
Working memory composite score	1.21	0.98–1.50	3.25	.0713	**1.38**	**1.18–1.61**	**16.20**	**.0001*****	1.03	0.92–1.15	0.21	.6505
Neurocognitive composite score	**1.34**	**1.10–1.64**	**8.27**	**.0040****	**1.49**	**1.28–1.73**	**27.00**	**.0001*****	1.05	0.94–1.18	0.82	.3643
Previous treatment												
Years since first antipsychotic treatment	**0.97**	**0.95–0.99**	**10.54**	**.0012****	**0.99**	**0.97–1.00**	**4.55**	**.0329***	0.99	0.98–1.00	1.27	.2592
Age at first antipsychotic treatment	1.01	0.99–1.04	1.52	.2172	1.01	0.99–1.02	0.33	.5673	**1.01**	**1.00–1.03**	**4.20**	**.0404***
No. of hospitalizations (lifetime)	0.92	0.81–1.04	1.78	.1827	1.00	0.91–1.10	0.00	.9948	**0.88**	**0.82–0.95**	**10.35**	**.0013****
No. of hospitalizations (past year)	0.95	0.77–1.17	0.27	.6039	1.02	0.88–1.18	0.07	.7861	**0.84**	**0.76–0.93**	**11.18**	**.0008*****
B. Multiple Regression												
Olanzapine									2.38	1.37–4.15	9.35	.0022
Living alone	2.38	1.42–3.98	10.82	.0010								
Treatment setting: state mental health	1.91	1.10–3.30	5.30	.0213	3.00	1.40–6.43	7.94	.0048				
Side effects (previous treatment)												
Constipation									0.52	0.33–0.82	7.96	.0048
Insomnia	0.47	0.27–0.82	7.20	.0073								
Rash									0.41	0.23–0.72	9.59	.0020
Total Movement Severity score									0.94	0.88–1.00	4.09	.0431
Calgary Depression Scale total score					0.80	0.73–0.87	26.89	.0001	0.93	0.89–0.97	10.67	.0011
Hopkins Verbal Learning Test	1.41	1.11–1.80	8.01	.0047								
Feeling about life in general	1.37	1.14–1.64	11.09	.0009								
Insight and Treatment Attitudes Questionnaire	1.09	1.02–1.16	7.38	.0066								
Previous treatment												
Years since first antipsychotic treatment	0.97	0.94–0.99	7.88	.0050								
No. of hospitalizations (past year)									0.78	0.65–0.92	8.52	.0035

[a]Values in bold font are significant at $P < .05$.
*$P < .05$. **$P < .01$. ***$P < .001$.
Abbreviations: DAI = Drug Attitude Inventory, OR = odds ratio, SF-12 = 12-Item Short-Form Health Survey.

Figure 1. Prognostic Subgroups for Remission, Response, and Treatment Continuation in Schizophrenia by 3 Months of Treatment



Abbreviations: HVLT = Hopkins Verbal Learning Test, ITAQ = Insight and Treatment Attitudes Questionnaire, SF-12 = 12-Item Short-Form Health Survey.

Table 3. Simple and Multiple Regression Analysis Stratified by Outcome Criteria by 6 Months of Treatment[a]

	Response				Remission				Continuation			
Baseline Characteristic	OR	95% CI	Wald	*P*	OR	95% CI	Wald	*P*	OR	95% CI	Wald	*P*
A. Bivariate regression												
Categorical characteristics												
Study medication												
Olanzapine	**2.04**	**1.39–2.98**	**13.46**	**.0002*****	0.58	0.42–0.79	0.25	.6787	**1.86**	**1.45–2.38**	24.05	.0001***
Quetiapine	0.78	0.49–1.24	1.09	.2955	0.96	0.68–1.37	0.04	.8382	**0.73**	**0.57–0.94**	**6.05**	.0139*
Risperidone	**0.57**	**0.35–0.93**	**5.13**	**.0235***	0.72	0.50–1.03	3.31	.0688	0.93	0.73–1.19	0.34	.5616
Male gender	0.71	0.48–1.05	2.94	.0862	**0.58**	**0.42–0.79**	**12.11**	**.0005*****	0.97	0.77–1.23	0.05	.8174
Race												
White	**1.66**	**1.12–2.47**	**6.23**	**.0126***	**1.40**	**1.04–1.90**	**4.80**	**.0285***	0.88	0.71–1.08	1.50	.2205
Black	**0.62**	**0.41–0.93**	**5.32**	**.0210***	**0.67**	**0.49–0.91**	**6.36**	**.0117***	1.05	0.85–1.30	0.20	.6517
Having close friends	1.33	0.91–1.95	2.13	.1442	**1.87**	**1.37–2.55**	**15.58**	**.0001*****	**1.41**	**1.14–1.75**	**10.23**	**.0014****
No additional help from family/friends	1.13	0.69–1.87	0.24	.6208	0.86	0.57–1.31	0.48	.4872	**1.38**	**1.02–1.86**	**4.48**	**.0343***
Being homeless	0.85	0.25–2.91	0.07	.7963	1.66	0.70–3.93	1.32	.2508	**0.43**	**0.23–0.78**	**7.53**	**.0061****
Comorbid conditions												
Major depressive disorder (current)	1.05	0.54–2.02	0.02	.8926	**0.51**	**0.29–0.89**	**5.54**	**.0186***	0.77	0.52–1.13	1.75	.1864
Panic disorder (past)	0.25	0.06–1.04	3.65	.0562	0.68	0.33–1.39	1.13	.2881	**0.62**	**0.39–0.99**	**3.95**	**.0468***
Obsessive-compulsive disorder (past)	1.31	0.62–2.77	0.50	.4815	0.79	0.41–1.55	0.45	.5004	**0.57**	**0.35–0.93**	**5.00**	**.0254***
Treatment setting												
Private	**3.01**	**1.31–6.90**	**6.79**	**.0092****	1.25	0.55–2.84	0.28	.5964	1.17	0.67–2.05	0.32	.5738
Research	0.39	0.12–1.26	2.49	.1148	**0.36**	**0.15–0.85**	**5.39**	**.0202***	**1.96**	**1.16–3.31**	6.26	.0123*
State mental health	1.99	1.31–3.02	10.46	.0012**	1.79	1.26–2.55	10.47	.0012**	0.68	0.52–0.89	7.99	**.0047****
Side effects (previous treatment)												
Constipation	1.06	0.65–1.72	0.05	.8161	**1.47**	**1.00–2.16**	**3.87**	**.0492***	0.74	0.55–1.00	3.74	.0530
Akinesia	0.92	0.59–1.44	0.14	.7087	0.81	0.57–1.17	1.22	.2694	**0.67**	**0.52–0.88**	**1.09**	**.0032****
Sleepiness	1.64	1.10–2.45	5.91	.0151**	1.39	1.01–1.92	4.08	.0435*	0.77	0.60–0.98	4.34	.0373*
Rash	**1.84**	**1.05–3.24**	**4.51**	**.0337***	0.81	0.47–1.39	0.60	.4402	0.91	0.60–1.37	0.21	.6436
Menstrual	2.16	1.07–4.37	**4.61**	**.0318***	**2.24**	**1.19–4.22**	**6.19**	**.0128***	1.09	0.63–1.90	0.09	.7619
Faintness	0.93	0.59–1.46	0.11	.7359	**0.65**	**0.45–0.96**	**4.78**	**.0288***	1.01	0.76–1.34	0.00	.9546
Continuous characteristics												
Age	**0.98**	**0.97–1.00**	**4.66**	**.0308***	1.00	0.99–1.01	0.01	.9387	**1.01**	**1.00–1.02**	**5.64**	**.0176***
Employment (3 = no, 1 = full-time)	0.96	0.69–1.33	0.06	.8015	**0.75**	**0.59–0.97**	**5.03**	**.0249***	1.04	0.86–1.25	0.16	.6927
Side effects (previous treatment)												
Abnormal Involuntary Movement Scale total score	0.94	0.87–1.01	2.73	.0982	**0.92**	**0.86–0.97**	**8.61**	**.0033****	0.98	0.94–1.01	1.98	.1590
Simpson-Angus Scale mean score	0.10	0.36–1.23	1.41	.2343	**0.44**	**0.26–0.74**	**9.77**	**.0018****	1.00	0.73–1.38	0.00	.9811
Calgary Depression Scale-suicidal ideation	1.34	0.95–1.89	2.74	.0980	**0.70**	**0.50–0.99**	**4.14**	**.0420***	**0.68**	**0.55–0.86**	**10.90**	**.0010*****
Calgary Depression Scale total score	1.03	0.99–1.07	1.77	.1840	**0.96**	**0.93–1.00**	**4.32**	**.0376***	**0.96**	**0.94–0.98**	**11.94**	**.0006*****
DAI total score (positive = compliant)	1.05	0.99–1.10	2.67	.1020	**1.06**	**1.02–1.11**	**7.68**	**.0056****	**1.05**	**1.02–1.08**	**13.66**	**.0002*****
Feeling about life in general	1.13	0.99–1.29	3.34	.0675	**1.19**	**1.07–1.33**	**10.53**	**.0012****	1.06	0.98–1.14	2.28	.1314
Insight and Treatment Attitudes Questionnaire	**1.07**	**1.02–1.11**	**8.12**	**.0044****	**1.06**	**1.03–1.10**	**12.49**	**.0004*****	1.02	1.00–1.04	3.24	.0720
Excessive drug use (0 = never –3 = often)	1.02	0.71–1.46	0.01	.9101	0.90	0.66–1.24	0.40	.5262	**0.79**	**0.64–0.98**	**4.47**	**.0346***
Neuropsychological measures												
Hopkins Verbal Learning Test	**1.28**	**1.06–1.54**	**6.85**	**.0089****	**1.49**	**1.28–1.73**	**25.96**	**.0001*****	1.05	0.95–1.17	0.89	.3446
Processing speed composite score	1.19	0.99–1.44	3.43	.0642	**1.56**	**1.33–1.82**	**31.20**	**.0001*****	**0.89**	**0.80–0.99**	**4.73**	**.0297***
Reasoning composite score	1.14	0.94–1.38	1.68	.1951	**1.19**	**1.02–1.39**	**5.03**	**.0249***	0.97	0.87–1.08	0.41	.5214
Working memory composite score	1.14	0.94–1.39	1.75	.1863	**1.38**	**1.17–1.62**	**14.79**	**.0001*****	0.95	0.86–1.06	0.75	.3863
Neurocognitive composite score	1.19	0.98–1.44	3.18	.0746	**1.47**	**1.25–1.71**	**23.00**	**.0001*****	0.95	0.86–1.06	0.73	.3945
Previous treatment												
Years since first antipsychotic treatment	**0.98**	**0.96–1.00**	**5.96**	**.0146***	0.98	0.97–1.00	5.49	.0191	1.00	0.99–1.01	0.13	.7220
Age at first behavioral treatment	1.00	0.97–1.02	0.25	.6188	**1.02**	**1.00–1.04**	**5.05**	**.0246***	1.01	1.00–1.02	1.91	.1667
Age at first antipsychotic treatment	1.00	0.98–1.02	0.11	.7399	**1.02**	**1.01–1.04**	**7.19**	**.0073***	**1.01**	**1.00–1.03**	5.40	.0202*
No. of hospitalizations (lifetime)	1.06	0.93–1.20	0.69	.4074	1.07	0.97–1.19	1.98	.1593	**0.899**	**0.836–0.965**	**8.5228**	.0035**
No. of hospitalizations (past year)	**1.20**	**1.01–1.43**	**4.24**	**.0394***	1.13	0.98–1.31	2.74	.0980	**0.852**	**0.768–0.945**	**9.2633**	**.0023****

(continued)

Table 3 (continued). Simple and Multiple Regression Analysis Stratified by Outcome Criteria by 6 Months of Treatment[a]

	Response				Remission				Continuation			
Baseline Characteristic	OR	95% CI	Wald	*P*	OR	95% CI	Wald	*P*	OR	95% CI	Wald	*P*
B. Multiple regression												
Olanzapine	1.94	1.24–3.05	8.34	.0039					1.70	1.03–2.82	4.23	.0398
Treatment setting												
State mental health	2.50	1.53–4.07	13.44	.0002								
Private	3.57	1.38–9.24	6.88	.0087								
Side effects (previous treatment)												
Sleepiness	1.66	1.08–2.54	5.35	.0208								
Menstrual					4.39	1.24–15.55	5.27	.0217				
Faintness					0.36	0.17–0.76	7.28	.0070				
Simpson-Angus Scale mean score					0.26	0.07–0.98	3.94	.0471				
Age	0.97	0.95–0.99	0.95	.0100								
Calgary Depression Scale total score									0.92	0.88–0.97	9.09	.0026
Calgary Depression Scale-suicidal ideation					0.45	0.23–0.90	5.04	.0248				
Insight and Treatment Attitudes Questionnaire	1.07	1.02–1.13	6.64	.0100								
Processing speed composite score					1.69	1.16–2.46	7.40	.0006	0.78	0.64–0.96	5.56	.0184
Previous treatment												
Years since first antipsychotic treatment					1.07	1.03–1.11	11.68	.0025	0.85	0.73–0.98	4.96	.0260
Age at first antipsychotic treatment					1.07	1.02–1.11	9.12	.0025				

[a]Values in bold font are significant at $P < .05$.
*$P < .05$. **$P < .01$. ***$P < .001$.
Abbreviations: DAI = Drug Attitude Inventory, OR = odds ratio.

Figure 2B displays hierarchical prognostic subgroups for remission at 6 months of treatment. Baseline clinical characteristics were able to identify subgroups with as low as a 14.8% likelihood of remission (HVLT *z* score < 0.2, Simpson-Angus Scale mean score ≥ 0.2, non-Hispanic) to as high as a 64.6% likelihood of remission (HVLT *z* score ≥ 0.2, female sex, age at first treatment for emotional problems ≥ 23 years). The most discriminative predictor of remission was HVLT *z* score at a threshold of 0.2 (n = 889, $\chi^2_1 = 29.908$, $P < .001$).

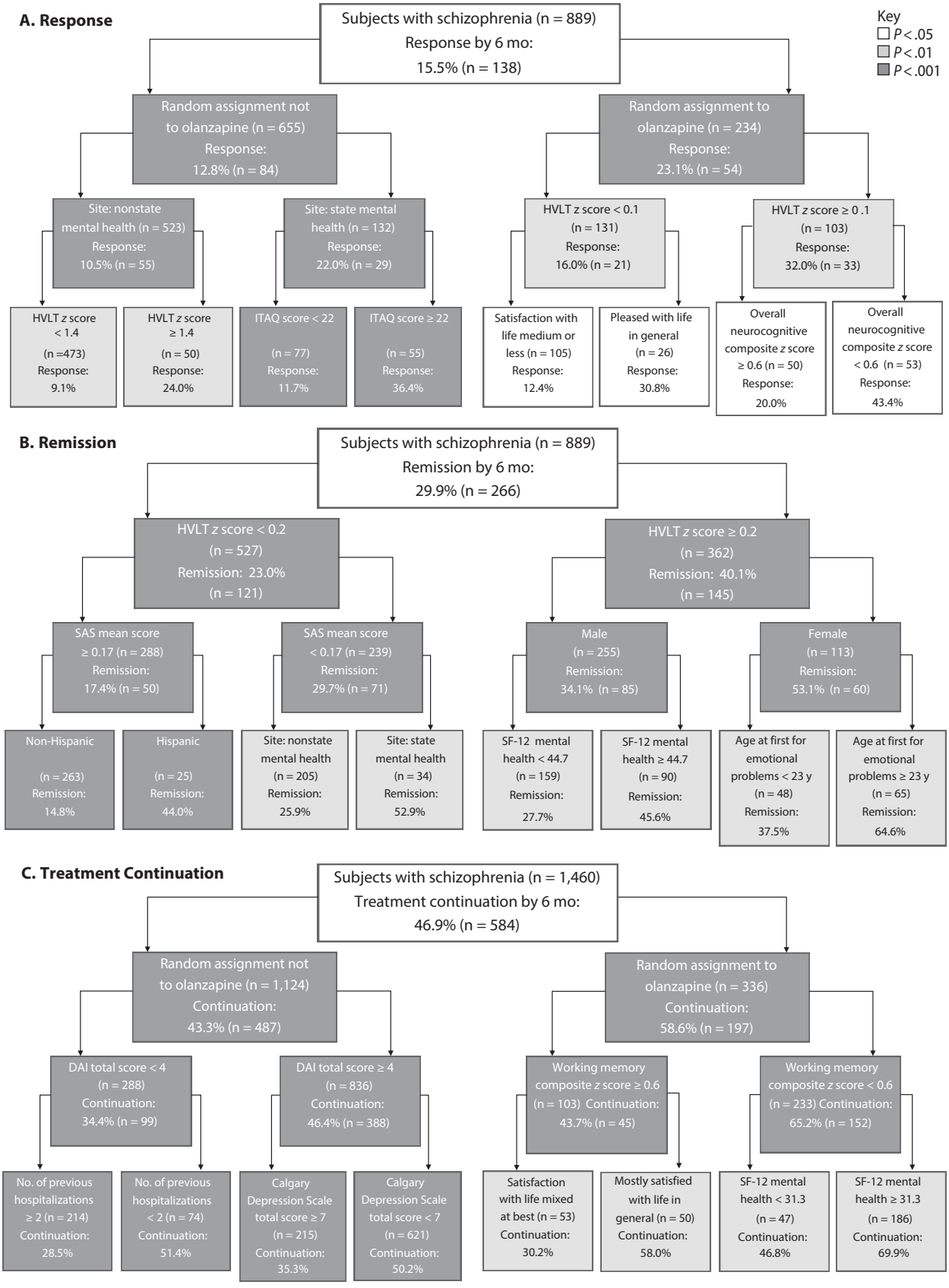
Figure 2C displays hierarchical prognostic subgroups for treatment continuation at 6 months of treatment. Baseline clinical characteristics were able to identify subgroups with as low as a 28.5% likelihood of continuing treatment (random assignment to a drug other than olanzapine, Drug Attitude Inventory total score < 4, number of previous hospitalizations ≥ 2) to as high as a 69.9% likelihood of continuing treatment (random assignment to olanzapine, working memory composite *z* score < 0.6, SF-12 mental health score ≥ 31.3). The most discriminative predictor of treatment continuation was random assignment to olanzapine (N = 1,460, $\chi^2_1 = 24.329$, $P < .001$).

DISCUSSION

Moderator analyses using both ROC analysis and logistic regression demonstrated that several baseline patient characteristics are predictive of response, remission, and treatment continuation in patients with schizophrenia. In particular, (1) baseline neuropsychological testing results; (2) previous reported side effects and medication attitudes; (3) psychosocial variables such as homelessness, living alone, and unemployment; (4) comorbid major depression or substance dependence; and (5) random assignment to olanzapine were particularly informative regarding patient outcomes. In multivariate logistic regression, baseline characteristics explained 16% and 18% of the variance in likelihood of remission at 3 and 6 months of antipsychotic treatment, respectively. At 6 months, ROC was able to differentiate patients based on baseline characteristics with a high likelihood of continuing with antipsychotic treatment (70%; random assignment to olanzapine, working memory composite *z* score < 0.6, SF-12 mental health score ≥ 31.3). Baseline characteristics were also able to identify patients with a relatively low likelihood of continuing with medication treatment at 6 months (29%; random assignment to a drug other than olanzapine, Drug Attitude Inventory total score < 4, number of previous hospitalizations ≥ 2).

Better performance on baseline neurocognitive testing across multiple domains (particularly verbal memory and overall composite scores) was strongly associated with likelihood of remission, medication response, and continuation of antipsychotic treatment. This finding is consistent with a well-established literature demonstrating associations between neurocognitive deficits and schizophrenia as well as improved neurocognitive performance as a predictor of treatment outcome. One of the largest meta-analytic studies[30] found significant performance

Figure 2. Prognostic Subgroups for Remission, Response, and Treatment Continuation in Schizophrenia by 6 Months of Treatment



Abbreviations: DAI = Drug Attitude Inventory, HVLT = Hopkins Verbal Learning Test, ITAQ = Insight and Treatment Attitudes Questionnaire, SAS = Simpson-Angus Scale, SF-12 = 12-Item Short-Form Health Survey.

deficits on 22 neurocognitive measures in schizophrenia patients compared to controls. Global verbal memory, performance IQ, full scale IQ, Continuous Performance Test scores, and word fluency were associated with the highest effect sizes ($d = 1.1–1.4$).[30] Participants of the CATIE trial displayed similar neurocognitive impairments when their scores were compared with a sample of healthy controls.[29] Meta-analytic data suggest verbal memory as a particularly good predictor of a variety of outcomes in schizophrenia.[31,32] In this analysis, we confirm the salience of neurocognitive characteristics for delineating prognostic and treatment assessment in schizophrenia. The finding of HVLT *z* score as the most discriminative predictor of remission at 3 and 6 months further underscores the importance of verbal memory dysfunction as a core cognitive deficit in schizophrenia. That it was able to predict remission relatively early in the course of treatment, while also being associated with 6-month response, can guide prognostic subtyping for developing more targeted approaches earlier in the course of treatment. Treatment incorporating cognitive remediation training is an active area of research and may hold promise in addressing outcome-relevant patient characteristics, such as the robust verbal memory findings highlighted in this and other analyses.

Consistent with the primary publications from the CATIE trial, random treatment assignment to olanzapine was associated with increased likelihood of antipsychotic continuation at 3 and 6 months.[5] This increased likelihood of continuation of olanzapine translated into an increased likelihood of treatment response after 6 months of treatment. Possible explanations for the superiority of olanzapine in the CATIE trial include increased tolerability and/or efficacy in the doses utilized compared to other antipsychotics included in the trial.[5] However, it is also important to acknowledge that the short-term benefits of olanzapine reported in this trial may be somewhat offset by the increased risk of more long-term side effects (eg, diabetes, metabolic syndrome, hyperlipidemia, and weight gain) compared to alternative antipsychotic medications.[33]

Patients' previous experiences with antipsychotic medications and baseline attitude regarding psychopharmacologic treatment were quite informative predictors regarding treatment outcome. Reports of increased side effects with previous treatment (akinesia, insomnia, faintness, rash, and dry mouth) were associated with decreased likelihood of medication continuation and 3-month treatment response and remission. Counterintuitively, increased reporting of several side effects at baseline (constipation, sleepiness, rash, menstrual problems, and faintness) was associated with increased likelihood of remission and response at 6 months, despite lower rates of treatment continuation. Perhaps reporting of these side effects indicated an ability to tolerate higher doses of antipsychotics in previous trials. More clearly, patients' attitude toward medications (as measured by the Drug Attitude Inventory) was strongly associated with treatment outcome early in treatment.[34] Positive attitudes toward medication in patients with schizophrenia have been previously demonstrated to be associated with medication adherence as well as lower level of psychotic symptoms, depressive symptoms, and higher quality of life.[35] Cognitive-behavioral therapies targeting treatment compliance in psychotic patients have been shown to be a useful tool in increasing medication attitudes and treatment adherence.[36]

Comorbid major depression was one of the best predictors of treatment continuation at 3 months in our analysis. Depression (50%) and substance abuse (47%) are the most frequent psychiatric comorbidities in psychotic patients.[37] Comorbid depression in schizophrenia has been previously associated with a higher probability of relapses and greater burden of symptom chronicity.[38,39] Below average SF-12 mental health score (< 50) was associated with worse treatment outcomes in this moderator analysis. Apart from being a general measure of mental health, the SF-12 was shown to be a useful diagnostic tool for detecting major depression in a large European sample.[40] Cutoff scores varying between 40 and 45 had a sensitivity of 0.86 and a specificity of 0.88 for diagnosing depressive disorders.[40] Therefore, we interpret both predictor variables, the *DSM-IV* diagnosis of major depression as well as the SF-12 mental health score, as indicators for depression.

Given the potentially important clinical findings of this secondary analysis of the CATIE trial, it is important to acknowledge several limitations of the analysis. The moderator analyses conducted in this article are exploratory and are not adjusted for multiple comparisons. None of our "significant findings," with the exception of several neuropsychological predictors of remission, would have survived a strict Bonferroni correction for multiple hypothesis testing. The prognostic subgroups identified using ROC methodology were empirically derived and not hypothesis driven. Thus, the exploratory findings from this analysis are for hypothesis-generating purposes and need to be replicated in secondary datasets. However, the statistical advantages of ROC analysis allowed the discovery of higher-order interactions in an exploratory way between clinical variables and the identification of homogenous prognostic subgroups based on easily ascertainable clinical characteristics. The value of the ROC analysis can be explained using the example of response at 3 months, where both the regression and the ROC identified processing speed to be a significant predictor. Only the ROC analysis indicated a cutoff score at which the predictive effect of processing speed was strongest (score of 0.9), whereas the regression assumed any interval on the predictor variable to be similarly predictive. Moreover, effects of interactions with other variables, such as the effects of private treatment setting, could be discovered only via ROC analysis.

In summary, our moderator analysis revealed several baseline predictors of antipsychotic treatment outcome in schizophrenia. Principal among these predictors were (1) neurocognitive testing; (2) previous reported side effects and patient attitude to medication; (3) comorbid depression and baseline mental health; (4) psychosocial factors such as unemployment, homelessness, and living alone; and

(5) random assignment to olanzapine versus the other antipsychotics. As these findings were a result of secondary, exploratory data analysis, they require replication. However, they suggest the possibility that treatment outcomes in schizophrenia may be improved not only by designing novel pharmacologic interventions but also by targeting interventions to improve (1) deficits in neuropsychological function, (2) patient attitudes toward medication, and (3) patients' social environment.

Submitted: June 17, 2014; accepted September 15, 2014.

Online first: September 15, 2015.

Drug names: clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa and others), quetiapine (Seroquel others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

Potential conflicts of interest: None reported.

Funding/support: The authors acknowledge the support of the National Institutes of Health (NIH) 1K23MH091240 (Dr Bloch), the Rembrandt Foundation (Dr Bloch), and UL1 RR024139 from the National Center for Research Resources, a component of the NIH, and NIH Roadmap for Medical Research (Dr Bloch). Data used in the preparation of this article were obtained from the limited-access datasets distributed from the NIH-supported Clinical Antipsychotic Trials of Intervention Effectiveness in Schizophrenia (CATIE-Sz). This is a multisite, clinical trial of persons with schizophrenia comparing the effectiveness of randomly assigned medication treatment. The study was supported by National Institute of Mental Health (NIMH) contract #N01MH90001 to the University of North Carolina at Chapel Hill. The ClinicalTrials.gov identifier is NCT00014001.

Role of the sponsor: The NIMH was responsible for monitoring the operations and conduct of the study and for reviewing and approving the manuscript. The Rembrandt Foundation funded a Tourette syndrome trial conducted by the authors and provided miscellaneous expenses that were used for salaries.

Disclaimer: This article reflects the views of the authors and may not reflect the opinions or views of the CATIE-Sz study investigators or the NIH.

Additional information: Readers can find details on how to access the CATIE public access database at http://www.nimh.nih.gov/funding/clinical-research/datasets/nimh-procedures-for-requesting-data-sets.shtml.

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