ORIGINAL ARTICLE

Neurocognitive Effects of Antipsychotic Medications in Patients With Chronic Schizophrenia in the CATIE Trial

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Context: Neurocognitive impairment in schizophrenia is severe and is an important predictor of functional outcome. The relative effect of the second-generation (atypical) antipsychotic drugs and older agents on neurocognition has not been comprehensively determined.

Objective: To compare the neurocognitive effects of several second-generation antipsychotics and a first-generation antipsychotic, perphenazine.

Design: Randomized, double-blind study of patients with schizophrenia assigned to receive treatment with olanzapine, perphenazine, quetiapine fumarate, or risperidone for up to 18 months as reported previously by Lieberman et al. Ziprasidone hydrochloride was included after its approval by the Food and Drug Administration.

Setting: Fifty-seven sites participated, including academic sites and treatment mental health facilities representative of the community.

Patients: From a cohort of 1460 patients in the treatment study, 817 completed neurocognitive testing immediately prior to randomization and then after 2 months of treatment.

Main Outcome Measures: The primary outcome was change in a neurocognitive composite score after 2 months of treatment. Secondary outcomes included neurocognitive composite score change at 6 months and 18 months after continued treatment and changes in neurocognitive domains.

Results: At 2 months, treatment resulted in small neurocognitive improvements of $z=0.13$ for olanzapine ($P<.002$), 0.25 for perphenazine ($P<.001$), 0.18 for quetiapine ($P<.001$), 0.26 for risperidone ($P<.001$), and 0.12 for ziprasidone ($P<.06$), with no significant differences between groups. Results at 6 months were similar. After 18 months of treatment, neurocognitive improvement was greater in the perphenazine group than in the olanzapine and risperidone groups. Neurocognitive improvement predicted longer time to treatment discontinuation, independently from symptom improvement, in patients treated with quetiapine or ziprasidone.

Conclusions: After 2 months of antipsychotic treatment, all groups had a small but significant improvement in neurocognition. There were no differences between any pair of agents, including the typical drug perphenazine. These results differ from the majority of previous studies, and the possible reasons are discussed.

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Group Information: The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study Investigators Group is listed on page 644.

NEUROCOGNITION IS SEVERELY impaired in patients with schizophrenia[1,2] independent of phase of illness.[3,4] While these impairments may appear prior to the onset of psychosis,[5-7] their severity in patients with chronic schizophrenia is about 1.5[8-10] to 2.0[11] SDs lower than the healthy population. Neurocognitive impairment is a central clinical feature of schizophrenia, because it is strongly associated with functional outcomes.[12,13]

The importance of neurocognition in schizophrenia is emphasized by large industry and government initiatives to develop new compounds to target neurocognitive impairment,[14] yet there are currently no approved treatments for neurocognitive impairment in schizophrenia

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and related disorders. The effect of newer-generation, "atypical" antipsychotic medications on neurocognition in patients with schizophrenia is controversial. While many studies[10,15-50] and meta-analyses[51-53] have suggested that second-generation antipsychotic treatment provides greater neu-

rocognitive benefit to patients with schizophrenia than first-generation, "typical" antipsychotics, many of these studies have had substantial weaknesses, such as small sample sizes, short duration of treatment, no comparator or a comparator of relatively high doses of first-generation antipsychotic treatment, and inattention to important clinical factors such as the relationship of cognitive improvement with symptom change, anticholinergic treatment, and change in extrapyramidal symptoms.[51-54] Further, many of these trials were industry sponsored, which has been argued recently to exert a biasing effect.[55] The impact of these various design weaknesses on study results is controversial.[52-54]

The observed associations between cognitive impairment and functional outcomes in patients with schizophrenia have offered promise that neurocognitive improvement will lead to functional benefit in these patients. Little is known about this relationship, and it is not clear if the neurocognitive benefit that may be provided by antipsychotic treatment will lead to improved treatment continuation.[56]

This National Institute of Mental Health–sponsored study Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) compared the neurocognitive effects of olanzapine, perphenazine, quetiapine fumarate, risperidone, and ziprasidone hydrochloride in patients with chronic schizophrenia. Our primary hypothesis was that neurocognitive response would be significantly different between these treatments. To maximize the statistical power for testing this hypothesis, our primary statistical tests focused on change in a single composite score after 2 months of treatment, during which improvement in neurocognition was expected based on previous studies. An additional hypothesis was that neurocognitive improvement in the early stages of treatment would predict treatment effectiveness as measured by time to all-cause discontinuation.

METHODS

STUDY SETTING AND DESIGN

The CATIE study was initiated by the National Institute of Mental Health to determine the comparative effectiveness of antipsychotic drugs. Its rationale, design, and methods were previously described[57-62] and the treatment effects on discontinuation rates and symptoms have been reported.[63] The study was conducted between January 2001 and December 2004 at 57 US clinical sites (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). Patients were randomized to receive olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone under double-blind conditions and studied for up to 18 months or until treatment was discontinued for any reason (phase 1). Patients whose assigned treatment was discontinued could receive other treatments in phases 2 and 3.[64,65] The present report is limited to phase 1 results.

PARTICIPANTS

Eligible patients were 18 to 65 years of age; had received a diagnosis of schizophrenia, as determined on the basis of the Structured Clinical Interview of the *DSM-IV*; and were able to take oral antipsychotic medication. Patients were excluded if they had a diagnosis of schizoaffective disorder, mental retardation, or other cognitive disorders; had a history of serious adverse reactions to the proposed treatments; had had only 1 schizophrenic episode; had a history of treatment resistance, defined by persistence of severe symptoms despite adequate trials of 1 of the proposed treatments or prior treatment with clozapine; were pregnant or were breastfeeding; or had a serious and unstable medical condition.

The study was approved by the institutional review board at each site, and written informed consent was obtained from the patients or their legally authorized representatives.

INTERVENTIONS

Identical-appearing capsules contained olanzapine (Zyprexa; Eli Lilly and Co, Indianapolis, Ind) (7.5 mg), quetiapine fumarate (Seroquel; AstraZeneca Pharmaceuticals LP, Wilmington, Del) (200 mg), risperidone (Risperdal; Janssen Pharmaceutica Products, Titusville, NJ) (1.5 mg), perphenazine (Trilafon; Schering-Plough, Kenilworth, NJ) (8 mg), or (after January 2002) ziprasidone hydrochloride (Geodon; Pfizer Inc, New York, NY) (40 mg). The packaging was done by Quintiles Inc, Research Triangle Park, NC. The dose of the medications was flexible, ranging from 1 to 4 capsules daily, based on the study physician's judgment. Relative tablet strength was reviewed by senior representatives from each drug manufacturer. Overlap in the administration of the antipsychotic agents that patients received before study entry was permitted for the first 4 weeks after randomization to allow a gradual transition to study medication. Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents. Patients had monthly visits with study doctors.

Because of product labeling, quetiapine and ziprasidone were given twice daily and olanzapine, perphenazine, and risperidone, once daily. To protect blinding, half the patients randomly assigned to perphenazine, olanzapine, and risperidone treatment were assigned to twice-daily dosing and half to once-daily dosing. To minimize initial adverse effects, patients assigned to quetiapine fumarate began treatment by receiving one 100-mg capsule on days 1 and 2, 1 twice daily on day 3, and 1 for the first dose of day 4. All patients assigned to twice-daily dosing received 5 identical-appearing capsules to begin treatment. Patients with current tardive dyskinesia (TD) as determined by a physician using Schooler-Kane criteria[63] were randomized to treatments other than perphenazine.

OBJECTIVES AND OUTCOMES

We hypothesized that there would be significant differences between olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone in improvement in cognition as measured by a neurocognitive composite score. As described in detail previously,[58,59] neurocognitive assessment with 11 tests was completed to produce a valid neurocognitive composite score in 1331 of 1460 patients at baseline. The 129 patients who did not complete baseline testing were very similar to those who completed testing on all symptom and demographic variables.[59] After 2 months in the study, 906 patients were still taking the medication to which they had been randomized, and 817 of them completed neurocognitive testing again (**Figure 1**). The neurocognitive tests were chosen by a group of advisors based on published standards, including sensitivity to impairment in schizophrenia, relation to functional outcome, potential sensitivity to treatment, and practicality for a large multisite schizophrenia antipsychotic clinical trial.[52,58,59] Testers were certified at an investigators' meeting, with fol-

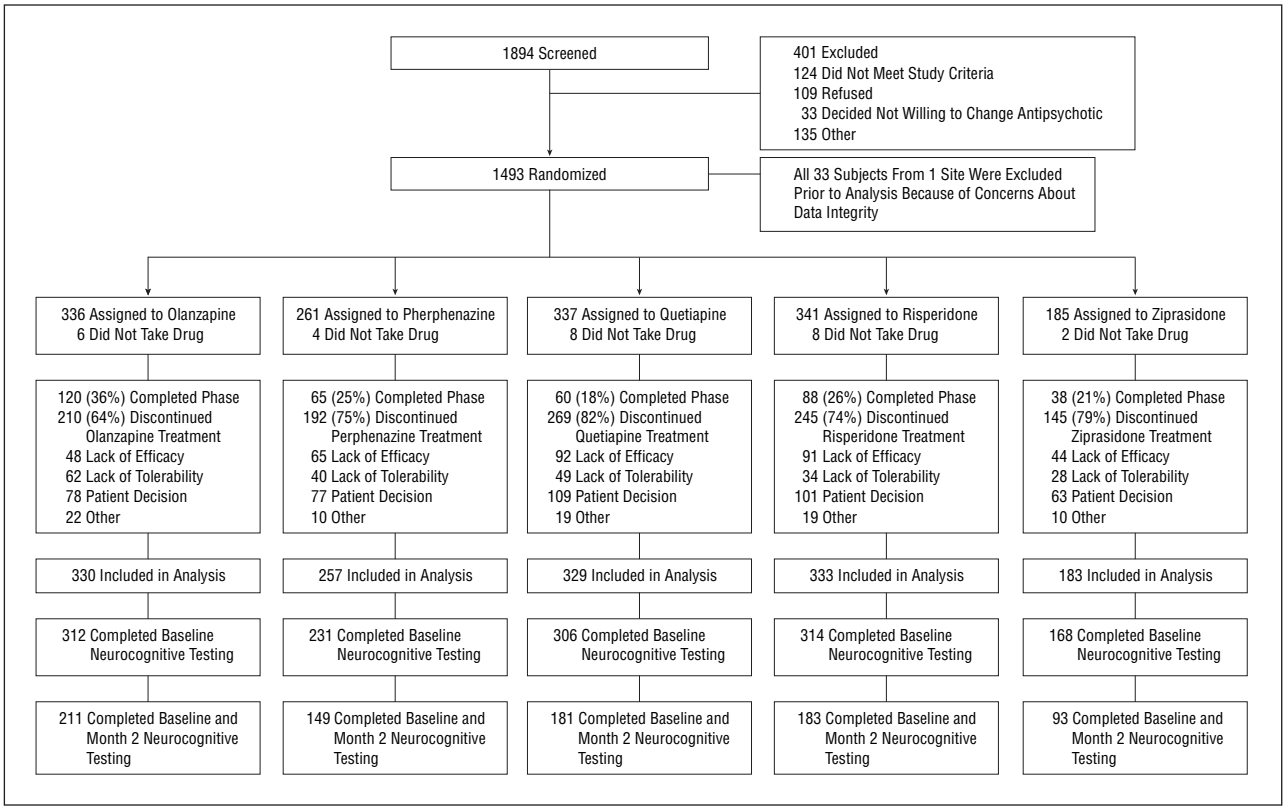

Figure 1. Enrollment, allocation, follow-up, and analysis. Quetiapine was given as quetiapine fumarate; ziprasidone, as ziprasidone hydrochloride.

low-up certification sessions throughout the study. Data quality was reviewed at a coordinating center.[58,59] Five neurocognitive domain scores were calculated from 9 neurocognitive test summary scores and standardized to create *z* scores (mean [SD], 0 [1]) for each domain. A neurocognitive composite score was calculated by creating a *z* score of the average of the 5 standardized domain scores.[59] Neurocognitive testing was also completed after 6 months and 18 months of continuing treatment with the same antipsychotic. The Pearson correlation between baseline and month 2 composite score was 0.85, indicating high within-subject consistency of the measure. Additional outcomes, collected at months 1, 3, 6, 9, 12, 15, and 18, included the incidence of neurologic adverse effects and scores on the Positive and Negative Syndrome Scale[66] (PANSS). Positive and Negative Syndrome Scale scores can range from 30 to 210, with higher scores indicating more severe psychopathology. Scores on the Wide Range Achievement Test, third edition,[67] reading subtest were used to estimate premorbid intellectual abilities.

STATISTICAL ANALYSES

The statistical plan was finalized prior to the initiation of analyses and posted on the CATIE Web site (http://www.catie.unc.edu/schizophrenia/documents/NeurocoganalysisplanFINALNov42005.pdf). Baseline characteristics for the 817 patients with a month 2 assessment were compared with the 514 patients who had baseline neurocognitive testing and did not complete month 2 testing in phase 1 using χ^2 tests or *t* tests. Treatment groups were also compared on these same parameters for the patients with month 2 data using χ^2 and analysis of variance tests. Within-group improvement in cognitive performance over time was evaluated with 1-sample *t* tests.

The primary objective was the comparison of treatment groups for the change in neurocognitive composite score from baseline to month 2. Secondary objectives included treatment comparisons for change in the 5 standardized domain scores at month 2. Statistical testing for changes at months 6 and 18 and for individual items is descriptive in nature. Treatment groups were compared using analysis of covariance (ANCOVA), adjusting for baseline score, whether the patient had required crisis stabilization in the 3 months prior to study entry, and TD status where applicable. All comparisons involving perphenazine excluded patients with TD. Because ziprasidone was added after approximately 40% of the patients had been enrolled, ziprasidone comparisons are secondary and were limited to the cohort of patients who underwent randomization after ziprasidone was added.

The composite score was evaluated for overall statistical significance between the 4 treatment groups at month 2 relative to $P = .05$ with the use of a test with 3 *df*, excluding patients with TD (data set 1). If the overall test result was significant, perphenazine was then compared with each of the atypical antipsychotics by a Hochberg modification[68] of the Bonferroni correction for multiple treatment comparisons, in which the largest *P* value was compared with .05 and the smallest *P* value was compared with .05/3 = .017. In addition, the 3 atypical drugs were compared with each other relative to $P \leq .05$ via step-down testing; pairwise comparisons were evaluated only if the *P* value from the 2 *df* test was $\leq .05$ (data set 2, patients with TD included). The ziprasidone group was compared with perphenazine and the other 3 atypical drugs within the ziprasidone cohort using a Hochberg adjustment for 4 treatment comparisons, in which the smallest *P* value was compared relative to .05/4 = .01 (data set 3, patients with TD excluded for comparison with perphenazine, and data set 4, patients with TD included).

Statistical significance of the domain scores was applied in the same manner as the composite, with 1 extra step. Overall significance for each domain was determined by using a

Table 1. Demographic and Baseline Characteristics of Patients With Neurocognitive Data

Variable	BL and Month 2 Data Available, No. (%) (n = 817)	BL Data Available but Month 2 Data Not Available, No. (%) (n = 514)	Comparison of Patients With Month 2 Data vs Those Without		BL and Month 18 Data Available, No. (%) (n = 294)
			t or χ^2 Statistic	*P* Value	
Age, y, mean (SD)	40.9 (10.8)	39.8 (11.2)	−1.84	.07	42.0 (11.2)
Patient's education, y, mean (SD)	12.2 (2.2)	12.0 (2.2)	−1.38	.17	12.2 (2.2)
Duration since first prescribed antipsychotic medication, y, mean (SD)	14.3 (10.8)	14.3 (10.3)	−0.11	.92	14.8 (11.3)
PANSS total score, mean (SD)	73.9 (17.5)	77.3 (17.2)	3.42	<.001	72.1 (17.2)
Mean modal dose, capsules, mean (SD)*	2.8 (1.0)	2.4 (0.9)	−6.68	<.001	2.8 (1.0)
Reached maximum dose	409 (50)	112 (26)	63.9	<.001	132 (45)
Sex					
M	610 (75)	380 (75)	0.06	.81	231 (79)
F	207 (25)	125 (25)			63 (21)
Race					
White	506 (62)	298 (59)	1.09	.30	197 (67)
Other	310 (38)	206 (41)			97 (33)
Ethnic origin					
Hispanic	89 (11)	56 (11)	0.01	.91	32 (11)
Marital status					
Married	90 (11)	67 (13)	1.88	.39	23 (8)
Previously married†	238 (29)	151 (30)			94 (32)
Never married	489 (60)	287 (57)			177 (60)
Employment status					
Unemployed	687 (84)	418 (84)	0.01	.90	243 (83)
Time to discontinuation, mo, mean (SD)	11.56 (6.38)	3.24 (1.54)	27.30	<.001	18.32 (0.87)
Baseline antipsychotic medications					
Olanzapine alone	200 (25)	102 (20)	3.86	.05	81 (28)
Quetiapine fumarate alone	53 (7)	33 (6)	<0.01	.96	18 (6)
Risperidone alone	171 (21)	85 (17)	3.92	.05	68 (23)
Any combination that includes olanzapine, quetiapine, or risperidone	69 (8)	52 (10)	1.07	.30	21 (7)
All others	123 (15)	90 (18)	1.41	.23	39 (13)
None	201 (25)	152 (30)	4.00	.05	67 (23)
Baseline neurocognitive composite and domain *z* scores (standardized in BL sample; n = 1331), mean (SD)					
Composite	0.00 (1.0)	0.00 (1.0)	−0.20	.85	0.00 (1.0)
Processing speed	−0.02 (1.0)	0.04 (1.1)	1.02	.31	−0.09 (1.0)
Reasoning	0.01 (1.0)	−0.02 (1.0)	−0.52	.61	0.03 (1.0)
Working memory	0.01 (1.0)	−0.01 (1.0)	−0.30	.76	0.01 (1.0)
Verbal memory	0.03 (1.0)	−0.06 (1.0)	−1.65	.10	0.07 (1.0)
Vigilance	−0.02 (1.0)	0.03 (1.0)	0.78	.44	0.01 (1.1)

Abbreviations: BL, baseline; PANSS, Positive and Negative Syndrome Scale.
*Dosing data for patients with only baseline data available are based on a sample of n = 423. One capsule corresponds to 7.5 mg of olanzapine, 200 mg of quetiapine fumarate, 1.5 mg of risperidone, 8 mg of perphenazine, and 40 mg of ziprasidone hydrochloride.
†Previously married includes widowed, divorced, or separated.

Hochberg adjustment for the number of domains, in which the largest *P* value was compared with .05 and the smallest *P* value was compared with .05/5 = .01. For each domain score, further adjustment for multiple treatment comparisons was then applied to the significance level assigned in the overall stage.

A sensitivity analysis of the ANCOVA model for the primary outcome evaluated the effects of potentially important baseline covariates such as site, demographic variables, clinical characteristics, alcohol and substance abuse, baseline medications, and their interactions with treatment group. The effect of post-baseline changes in PANSS, Abnormal Involuntary Movement Scale,[69] and Barnes and Simpson-Angus scale[70] scores; compliance; and the addition of anticholinergic treatment on the primary outcome at month 2 were examined using ANCOVA and Pearson correlation. Lastly, Cox proportional hazards regression was used to evaluate whether change in the composite score from baseline to month 2 was a predictor of subsequent time to discontinuation for any reason and for lack of efficacy. The analysis followed the same strategy described earlier in the primary ANCOVA model and also adjusted for baseline composite score, as well as PANSS baseline score and change from baseline to month 1.

The power for finding a meaningful difference in neurocognitive change between any pair of treatment groups, identified as one quarter of the baseline standard deviation, was approximately 97% for the primary composite score, based on a sample size of 150 per treatment group and a standard deviation for change from baseline of 0.55 (obtained from month 2 results). For the domain scores, power estimates for finding any pairwise treatment difference ranged from 66% (SD 0.90%) to 82% (SD 0.75%).

RESULTS

CHARACTERISTICS AND DISPOSITION OF PATIENTS

The enrollment, allocation, and follow-up of study patients were described previously.[63] One thousand four hundred ninety-three patients were enrolled in the study and randomized to treatment. Data from 33 subjects at 1 site were excluded prior to analysis for poor integrity. The 1331 patients who were tested at baseline were found in previously published analyses to be very similar on demographic measures to the total number of 1460 patients who were entered into the study,[59] and this conclusion applies to the current cohort of 817 patients who completed neurocognitive testing at baseline and at the primary end point, 2 months postbaseline. This group of patients is the primary cohort for this report. At baseline, 25% of patients reported being antipsychotic-free, 60% of patients were taking second-generation antipsychotics, 10% were taking first-generation antipsychotics, and 5% were taking a combination of first- and second-generation antipsychotics. The percentages of patients who were randomized to the same drug they reported taking at baseline are as follows: olanzapine, 30%; perphenazine, 0%; quetiapine, 10%; risperidone, 24%; and ziprasidone, 4%. The baseline demographic and clinical characteristics of the primary cohort and those who were tested at baseline but not at 2 months (n=514) are described in **Table 1**. Patients who were tested at baseline and month 2 had lower PANSS scores and higher doses during the course of phase 1. The other measures, including neurocognitive composite and domain scores, were not different between groups. The primary cohort was representative of the population of patients with chronic schizophrenia except there were fewer women (25%). Patients who completed testing at baseline and 18 months were very similar to the primary cohort.

Mean modal doses during the entire course of phase 1 for the patients who had neurocognitive test data at baseline and 2 months were olanzapine, 21.0 mg/d; perphenazine, 21.5 mg/d; quetiapine fumarate, 566.3 mg/d; risperidone, 4.1 mg/d; and ziprasidone hydrochloride, 121.9 mg/d. Mean modal doses at month 2 were very similar but slightly lower: olanzapine, 19.6 mg/d; perphenazine, 20.3 mg/d; quetiapine fumarate, 528.3 mg/d; risperidone, 3.9 mg/d; and ziprasidone hydrochloride, 117.4 mg/d. The doses of the second-generation drugs are similar to what is found in clinical practice,[71,72] although the doses of olanzapine and quetiapine are about 30% higher. Seventy-four percent of patients discontinued their assigned treatment in phase 1 prior to 18 months, with a median time of 6 months. Because treatment discontinuation differed between treatments,[63] the percentage of patients who provided neurocognitive data at the 2-month assessment also differed between treatments as follows: olanzapine, 68%; perphenazine, 65%; quetiapine, 59%; risperidone, 58%; and ziprasidone, 55%. Mean modal doses for the patients who had neurocognitive test data at baseline and 18 months were olanzapine, 20.5 mg/d; perphenazine, 22.0 mg/d; quetiapine fumarate, 596.3 mg/d; risperidone, 4.1 mg/d; and ziprasidone hydrochloride, 118.7 mg/d.

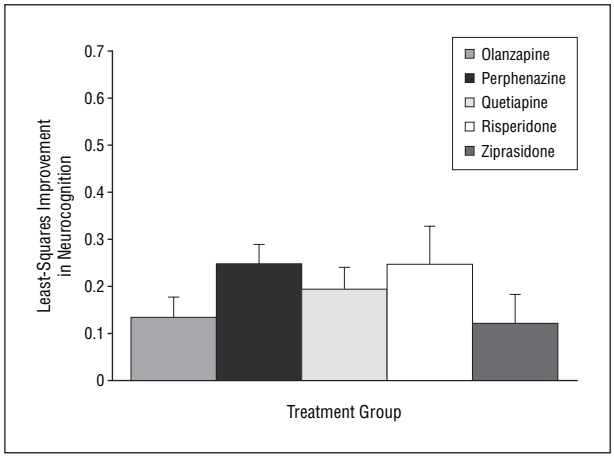

Figure 2. Least-squares mean improvement in neurocognitive composite score after 2 months of antipsychotic treatment, adjusted for baseline score and whether the patient required crisis stabilization in the 3 months prior to study entry. Patients with tardive dyskinesia were not included in the data presented in this figure (data set 1). Only the ziprasidone hydrochloride data were from data set 3, collected when ziprasidone became available, after 40% of the patients had already been entered into the study. Quetiapine was given as quetiapine fumarate.

NEUROCOGNITIVE EFFECTS OF TREATMENT

Neurocognitive Changes After 2 Months of Treatment

Change in the neurocognitive composite score from baseline to 2 months, the primary outcome measure in this study, showed improvement in each of the treatment groups. In the primary set of patients without TD (data set 1), treatment resulted in the following composite score improvements: olanzapine, 0.13 ($P<.002$); perphenazine, 0.25 ($P<.001$); quetiapine, 0.18 ($P<.001$); and risperidone, 0.26 ($P<.001$). (Least-squares means are presented in **Figure 2**; means are presented in **Table 2**). There was no overall difference between the treatment groups ($P=.20$). When patients with TD were included in the analysis (data set 2) and TD was used as an additional covariate in the analysis, the results were similar, with composite score improvements of 0.13 for olanzapine, 0.14 for quetiapine, and 0.22 for risperidone. Patients with TD had less overall improvement than those without TD ($t_{573}=2.33$; $P=.02$). However, the TD × treatment group interaction for neurocognitive composite score change was not statistically significant ($P=.27$). Within the cohort of 463 patients who underwent randomization after ziprasidone was added to the trial, the results were similar and not statistically significant between groups. The ziprasidone group had improvements of 0.12 ($P<.06$) when patients with TD were excluded (data set 3) and 0.18 ($P<.001$) when they were included (data set 4).

Treatment analyses were also completed with site, Wide Range Achievement Test reading score, years of education, and baseline alcohol and substance use included in the model. These covariates did not produce statistics that differed from the unadjusted analyses.

A model of prediction of improvement in neurocognitive composite score from baseline to 2 months ($R^2=0.19$) suggested that lower baseline composite score

Table 2. Change in Neurocognitive Composite *z* Scores and Domain *z* Scores From Baseline to Month 2 by Treatment*

	z Score, Mean (SD)					F Test; *P* Value; Paired Comparison
	Olanzapine	Perphenazine	Quetiapine	Risperidone	Ziprasidone	
Data set 1†	n = 163	n = 149	n = 146	n = 151		
Composite score	0.13 (0.52)	0.25 (0.57)‡	0.18 (0.51)	0.26 (0.62)	NA	1.54; .20; NS§
Processing speed	0.15 (0.52)	0.18 (0.54)‡	0.21 (0.57)	0.13 (0.54)	NA	1.06; .37; NS§
Reasoning	0.11 (0.65)	0.20 (0.74)‡	0.08 (0.67)	0.22 (0.72)	NA	1.27; .28; NS§
Working memory	0.10 (0.70)	0.18 (0.78)‡	0.05 (0.78)	0.26 (0.87)	NA	0.82; .48; NS§
Verbal memory	–0.01 (0.86)	0.17 (0.92)‡	–0.01 (0.86)	0.15 (0.95)	NA	2.26; .08; NS§
Vigilance	0.19 (0.73)	0.24 (0.76)‡	0.37 (0.78)	0.30 (0.84)	NA	1.41; .24; NS§
Data set 2‖	n = 211		n = 181	n = 183		
Composite score	0.13 (0.53)‡	NA	0.14 (0.54)‡	0.22 (0.60)‡	NA	0.89; .41; NS§
Processing speed	0.14 (0.53)‡	NA	0.18 (0.58)‡	0.08 (0.54)‡	NA	1.98; .14; NS§
Reasoning	0.10 (0.66)‡	NA	0.03 (0.70)‡	0.21 (0.69)‡	NA	2.69; .07; NS§
Working memory	0.09 (0.70)‡	NA	0.04 (0.75)‡	0.20 (0.86)‡	NA	1.09; .34; NS§
Verbal memory	–0.02 (0.87)‡	NA	–0.02 (0.88)‡	0.13 (0.95)‡	NA	1.45; .23; NS§
Vigilance	0.20 (0.74)‡	NA	0.34 (0.76)‡	0.27 (0.81)‡	NA	0.94; .39; NS§
Data set 3¶		n = 81			n = 74	
Composite score	NA	0.26 (0.63)	NA	NA	0.12 (0.51)	NA
Processing speed	NA	0.16 (0.59)	NA	NA	0.03 (0.38)	NA
Reasoning	NA	0.19 (0.70)	NA	NA	0.15 (0.67)	NA
Working memory	NA	0.20 (0.81)	NA	NA	0.18 (0.67)	NA
Verbal memory	NA	0.22 (0.95)	NA	NA	–0.08 (0.91)	NA
Vigilance	NA	0.29 (0.89)	NA	NA	0.16 (0.52)	NA
Data set 4#	n = 100		n = 99	n = 90	n = 93	
Composite score	0.10 (0.51)	NA	0.25 (0.52)	0.23 (0.55)	0.18 (0.54)‡	NA
Processing speed	0.14 (0.61)	NA	0.26 (0.53)	0.07 (0.53)	0.08 (0.40)‡	NA
Reasoning	0.06 (0.67)	NA	0.09 (0.66)	0.26 (0.72)	0.14 (0.69)‡	NA
Working memory	0.10 (0.64)	NA	0.14 (0.79)	0.20 (0.80)	0.24 (0.70)‡	NA
Verbal memory	–0.05 (0.80)	NA	0.07 (0.97)	0.23 (0.89)	0.01 (0.97)‡	NA
Vigilance	0.15 (0.71)	NA	0.43 (0.73)	0.19 (0.80)	0.24 (0.64)‡	NA

Abbreviations: NA, not applicable; NS, not significant; TD, tardive dyskinesia.
*The sample size varies because of sporadic missing data; the sample size for "vigilance" was the most reduced, with a mean reduction of 13.7% per group in each comparison. Quetiapine was given as quetiapine fumarate; ziprasidone, as ziprasidone hydrochloride.
†Perphenazine vs olanzapine, quetiapine, and risperidone excluding patients with TD and patients taking ziprasidone.
‡Treatment conditions of primary interest in each data set.
§The tests were not performed since the overall *P* value did not meet the criterion for significance as described in the statistical plan.
‖Olanzapine vs quetiapine vs risperidone including patients with TD, excluding patients taking ziprasidone or perphenazine.
¶Ziprasidone vs perphenazine excluding patients with TD, including patients taking ziprasidone.
#Ziprasidone vs olanzapine, quetiapine, and risperidone including patients with TD and patients taking ziprasidone.

($P<.001$), higher Wide Range Achievement Test reading score ($P<.001$), presence of substance abuse at baseline ($P=.002$), better compliance ($P=.003$), greater improvement in PANSS Negative Symptom Scale scores at 1 month ($P=.007$), absence of TD ($P=.01$), and site ($P=.01$) were all significant predictors of greater cognitive improvement.

Change With Treatment in Neurocognitive Domain Scores and Individual Outcome Measures

Figure 3 and Table 2 present the changes in the 5 neurocognitive domains from baseline to 2 months. There was no significant disparity between the groups in improvement across the neurocognitive domains (all *P* values >.08).

Since there were no differences between treatment groups on the neurocognitive composite and domain scores, presentation of the individual measures at baseline and month 2 includes the entire cohort collapsed across treatment groups (**Table 3**). Change in the individual measures was small but consistently positive.

Neurocognitive Change After 6 Months of Treatment

There were 523 patients who completed neurocognitive testing at baseline and then 6 months later while still receiving the medication to which they had been randomized. In the original analytic plan, the comparisons at 6 months were considered exploratory and thus not eligible for statistical thresholds for significance. The neurocognitive composite score improved ($P<.001$) for each of the treatment groups from baseline to 6 months of treatment. There were no differences between the groups on the change in the neurocognitive composite score ($P=.35$) or any of the neurocognitive domains (all *P* values >.01).

Neurocognitive Change After 18 Months of Treatment

A total of 303 patients were tested at 18 months while still receiving the medication to which they had originally been randomized. Thus, 37% of the patients from the 2-month analyses were included. The 303 patients

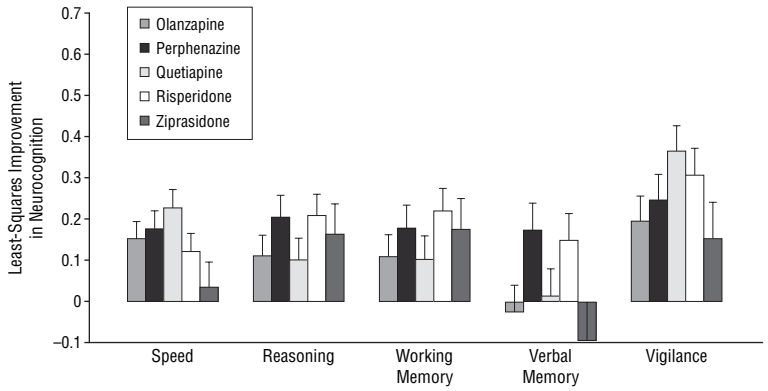

Figure 3. Least-squares mean improvement in neurocognitive domain scores after 2 months of antipsychotic treatment, adjusted for baseline score and whether the patient required crisis stabilization in the 3 months prior to study entry. Patients with tardive dyskinesia were not included in the data presented in this figure (data set 1). Only the ziprasidone hydrochloride data were from data set 3, collected when ziprasidone became available, after 40% of the patients had already been entered into the study. Quetiapine was given as quetiapine fumarate.

Table 3. Neurocognitive Raw Scores for 817 Patients With Both a Baseline and a Month 2 Composite Score

	Baseline		Month 2	
Variable	**No.**	**Mean (SD)**	**No.**	**Mean (SD)**
COWAT[73] score				
F words	816	9.7 (4.1)	817	9.9 (4.0)
A words	816	7.8 (3.6)	817	7.9 (3.7)
S words	816	9.9 (4.3)	816	10.0 (4.3)
Sum	816	27.5 (10.6)	817	27.8 (10.8)
Category Instances[73] score				
Animals	817	14.0 (5.0)	817	14.1 (4.8)
Fruits	817	10.2 (3.4)	816	10.2 (3.6)
Vegetables	817	8.7 (3.4)	816	8.8 (3.5)
Sum	817	32.8 (10.0)	817	33.0 (10.3)
WISC-III Mazes[74] score	808	17.6 (5.8)	810	18.2 (5.7)
Letter-Number Sequencing[75] score	812	10.2 (4.4)	814	10.9 (4.4)
Hopkins Verbal Learning Test[76] score				
Trial 1	816	4.8 (1.8)	816	4.9 (1.8)
Trial 2	816	6.5 (2.1)	815	6.7 (2.2)
Trial 3	817	7.6 (2.4)	815	7.7 (2.4)
WAIS-R[77] digit symbol score	817	37.2 (13.0)	816	38.8 (13.9)
Grooved Pegboard[78] score				
Trial 1	813	11.7 (3.9)	811	12.5 (4.0)
Trial 2	813	13.2 (4.0)	809	13.7 (4.1)
CPT d′[79] score				
2 Digit	672	2.339 (1.032)	720	2.602 (0.998)
3 Digit	674	1.781 (0.915)	709	1.984 (0.947)
4 Digit	659	1.010 (0.744)	679	1.136 (0.805)
Visuospatial Working Memory[80] test score				
No delay condition	745	2.4 (3.1)	762	2.5 (3.1)
5-s Condition	745	27.8 (18.6)	762	26.7 (16.5)
15-s Condition	745	30.3 (18.9)	762	29.5 (18.1)
Mean of 5- and 15-s condition minus no delay	745	26.7 (17.4)	762	25.6 (15.8)
Wisconsin Card Sorting Test–64[81] score				
Preservative errors	781	13.5 (10.1)	785	12.0 (9.3)
Categories completed	780	2.1 (1.6)	785	2.3 (1.7)
Categories completed + additional cards in final category	780	2.34 (1.71)	785	2.46 (1.77)

Abbreviations: COWAT, Controlled Oral Word Association Test; CPT, Continuous Performance Test, identical pairs; WAIS-R, Wechsler Adult Intelligence Test–Revised Edition; WISC-III, Wechsler Intelligence Scale for Children, Third Edition.

represent only 21% of the 1460 patients entered into the trial. Comparisons were made to determine if the 303 patients who continued for 18 months taking the medication to which they had been randomized were different from the other patients (n=1028) on the neurocognitive scores at baseline. There were no significant differences on the composite score or any of the individual domains (all P values $>.05$), suggesting that the patients in these analyses are representative of the entire cohort in terms of baseline neurocognition. The percentage of patients who provided neurocognitive data at the 18-month assessment differed between treatments as fol-

Table 4. Change in Neurocognitive Composite *z* Scores and Domain *z* Scores From Baseline to Month 18 by Treatment*

	z Score, Mean (SD)					F Test; *P* Value
	Olanzapine	Perphenazine	Quetiapine	Risperidone	Ziprasidone	
Data set 1†	n = 74	n = 52	n = 46	n = 55		
Composite score	0.15 (0.54)	0.49 (0.71)‡	0.35 (0.58)	0.28 (0.75)	NA	3.63; .01
Processing speed	0.24 (0.48)	0.41 (0.72)‡	0.43 (0.69)	0.27 (0.64)	NA	1.40; .24
Reasoning	0.20 (0.80)	0.51 (0.74)‡	0.13 (0.76)	0.17 (0.89)	NA	3.44; .02
Working memory	0.00 (0.73)	0.33 (0.80)‡	0.05 (0.75)	0.26 (1.00)	NA	2.35; .07
Verbal memory	–0.09 (0.85)	0.18 (1.04)‡	0.21 (0.98)	0.14 (1.03)	NA	2.18; .09
Vigilance	0.23 (0.86)	0.46 (0.69)‡	0.58 (0.83)	0.30 (0.99)	NA	2.27; .08
Data set 2§	n = 90		n = 54	n = 67		
Composite score	0.18 (0.58)‡	NA	0.33 (0.61)‡	0.25 (0.74)‡	NA	1.02; .36
Processing speed	0.26 (0.48)‡	NA	0.44 (0.67)‡	0.23 (0.70)‡	NA	2.20; .11
Reasoning	0.23 (0.78)‡	NA	0.11 (0.79)‡	0.21 (0.86)‡	NA	0.04; .96
Working memory	0.02 (0.81)‡	NA	0.03 (0.75)‡	0.18 (1.02)‡	NA	0.44; .64
Verbal memory	–0.05 (0.86)‡	NA	0.17 (0.98)‡	0.09 (1.02)‡	NA	1.21; .30
Vigilance	0.26 (0.82)‡	NA	0.55 (0.84)‡	0.28 (0.98)‡	NA	1.92; .14
Data set 3‖		n = 27			n = 23	
Composite score	NA	0.42 (0.52)	NA	NA	0.33 (0.62)	NA
Processing speed	NA	0.38 (0.67)	NA	NA	0.17 (0.68)	NA
Reasoning	NA	0.39 (0.62)	NA	NA	0.32 (0.63)	NA
Working memory	NA	0.28 (0.73)	NA	NA	0.44 (0.74)	NA
Verbal memory	NA	0.03 (0.89)	NA	NA	–0.04 (1.03)	NA
Vigilance	NA	0.53 (0.72)	NA	NA	0.43 (0.86)	NA
Data set 4¶	n = 41		n = 25	n = 31	n = 31	
Composite score	0.13 (0.48)	NA	0.31 (0.68)	0.13 (0.67)	0.37 (0.60)‡	NA
Processing speed	0.27 (0.45)	NA	0.35 (0.63)	0.16 (0.59)	0.25 (0.71)‡	NA
Reasoning	–0.06 (0.71)	NA	0.12 (0.83)	0.16 (0.88)	0.35 (0.59)‡	NA
Working memory	0.11 (0.76)	NA	–0.02 (0.90)	0.15 (1.00)	0.41 (0.73)‡	NA
Verbal memory	–0.04 (0.90)	NA	0.12 (0.85)	0.04 (1.05)	–0.04 (1.04)‡	NA
Vigilance	0.25 (0.61)	NA	0.68 (0.94)	0.04 (0.89)	0.46 (0.83)‡	NA

Abbreviation: NA, not applicable.

*The sample size varies because of sporadic missing data; the sample size for "vigilance" was the most reduced, with a mean reduction of 12.9% per group in each comparison. Quetiapine was given as quetiapine fumarate; ziprasidone, as ziprasidone hydrochloride.

†Perphenazine vs olanzapine, quetiapine, and risperidone excluding patients with TD and patients taking ziprasidone.

‡Treatment conditions of primary interest in each data set.

§Olanzapine vs quetiapine vs risperidone including patients with TD, excluding patients taking ziprasidone or perphenazine.

‖Ziprasidone vs perphenazine excluding patients with TD, including patients taking ziprasidone.

¶Ziprasidone vs olanzapine, quetiapine, and risperidone including patients with TD and patients taking ziprasidone.

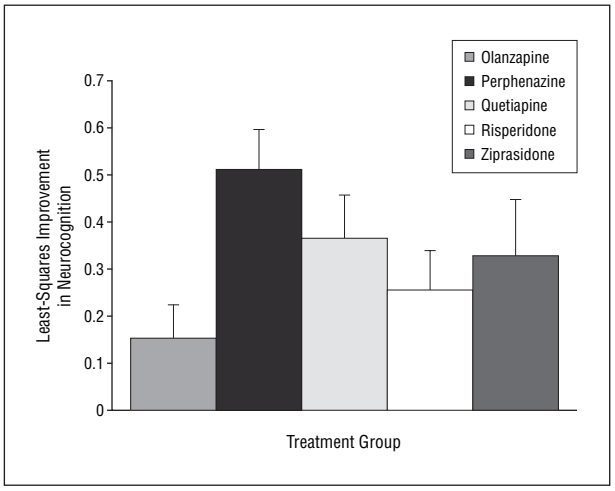

Figure 4. Least-squares mean improvement in neurocognitive composite score after 18 months of antipsychotic treatment, adjusted for baseline score and whether the patient required crisis stabilization in the 3 months prior to study entry. Patients with tardive dyskinesia were not included in the data presented in this figure (data set 1). Only the ziprasidone hydrochloride data were from data set 3, collected when ziprasidone became available, after 40% of the patients had already been entered into the study. Quetiapine was given as quetiapine fumarate.

lows: olanzapine, 29%; perphenazine, 23%; quetiapine, 18%; risperidone, 21%; and ziprasidone, 18%.

In the original analytic plan, the comparisons at 18 months were considered exploratory and thus not eligible for statistical thresholds for significance. In patients without TD, there were improvements in the neurocognitive composite score from baseline in all of the treatment groups (**Table 4** and **Figure 4**). The improvement in the composite score from month 2 to month 18 was 0.11 (t_{273}=3.20; $P \leq 0.01$), suggesting that most of the cognitive improvement occurred in the first 2 months of treatment.

There were overall differences between treatments in composite score change ($P<.05$). Pairwise comparisons suggested that improvement in the neurocognitive composite score was greater in the perphenazine group (0.49) than in the olanzapine group (0.15; $P=.002$) or the risperidone group (0.28; $P=.04$). The ziprasidone and quetiapine groups did not differ from any of the other treatments.

Some of the overall differences between groups were explained by the differences in the reasoning domain, although this difference would not have met the criteria for formal statistical significance after controlling for mul-

Table 5. Pearson Correlations Between Cognitive Change and Clinical Change From Baseline*

	PANSS Score Change at 1 Month				PANSS Score Change at 3 Months			
	Total	Positive	Negative	General	Total	Positive	Negative	General
Change in composite score at 2 mo	–0.03	–0.08	–0.06	–0.07	–0.08	–0.13	–0.10	–0.15

Abbreviation: PANSS, Positive and Negative Syndrome Scale.
*Correlations greater than $r = 0.08$ had $P<.05$; greater than $r = 0.10$, $P<.01$; and greater than $r = 0.12$, $P<.001$.

tiple comparisons. The perphenazine group tended to improve more than the other treatment groups (Table 4). In comparisons between the second-generation treatments that included patients with TD, there were no overall differences between the groups.

Associations Between Cognitive Change From Baseline and Other Clinical Changes

The Pearson correlations between change in neurocognitive composite score from baseline and change in PANSS symptom factors from baseline are listed in **Table 5**. Negative correlations indicate that cognitive improvement was associated with symptom reduction, but the magnitude of these correlations was quite small. The correlations between change in neurocognitive composite score from baseline to 2 months and the 1-month and 3-month changes from baseline in extrapyramidal symptoms (Simpson-Angus scale mean score), TD (Abnormal Involuntary Movement Scale global severity score), and akathisia (Barnes scale global score) were $r<0.05$ with all P values $>.05$. The correlation between neurocognitive change and compliance was 0.07 ($P=.04$). The 151 patients who were receiving anticholinergic medications at baseline had a mean neurocognitive score change of 0.169, which did not differ from the 666 patients who were not receiving anticholinergic medications at baseline, who had a mean score change of 0.224. However, for the 38 patients who had anticholinergic medications added during the first 2 months of treatment, composite scores worsened (mean [SD] change, –0.049 [0.46]) at the 2-month assessment, compared with other patients whose composite scores improved (mean [SD] change, 0.190 [0.56]) ($P\leq0.01$). No interaction between neurologic or anticholinergic measures and treatment group was found for the composite score.

Neurocognitive Predictors of Treatment Discontinuation

Cox proportional hazards regression analyses suggested that change in the neurocognitive composite score from baseline to 2 months was not a significant predictor of time until all-cause discontinuation. However, there was a suggestion of a treatment interaction for this analysis ($P<.10$). Neurocognitive improvement predicted time to all-cause discontinuation in patients treated with quetiapine ($P=.02$; hazard ratio for 0.25-SD improvement in composite score, 0.98 [95% confidence interval, 0.954-0.996]) and ziprasidone ($P=.009$; hazard ratio, 0.957 [95% confidence interval, 0.925-0.989]) but not the other treatments. Inclusion of change in PANSS score, compliance, and other baseline covariates found previously to predict time to discontinuation did not reduce the statistical significance for the quetiapine group. The prediction of time to discontinuation due to inefficacy produced similar results.

COMMENT

All of the antipsychotic treatment groups had a small improvement in neurocognition as measured by change in a composite score derived from 11 neurocognitive tests assessed at baseline and after 2 months of treatment. However, there was no significant difference between the groups. Exploratory analyses suggested that after 18 months of treatment, there might be differences between the treatments, with the older antipsychotic perphenazine demonstrating the most neurocognitive improvement. Neurocognitive improvement was found to contribute to the overall effectiveness of some of the antipsychotic treatments as measured by time to discontinuation. A variety of demographic and clinical factors contributed to neurocognitive improvement.

The current results are in contrast to numerous published studies and 3 meta-analyses suggesting neurocognitive advantages of the second-generation antipsychotic medications compared with first-generation treatments.[10,15-53] This failure to document a neurocognitive advantage of second-generation antipsychotics suggests that the positive findings from prior reports may not generalize well to the type of everyday clinical practice examined in the CATIE trial. The contrast between the current results and those reported previously may be explained in part by methodological differences between the studies; thus, careful scrutiny is warranted.[51-54]

First, the current study included neurocognitive treatment data on 817 patients, more than twice as many as the largest previous trial. It is possible that smaller studies are susceptible to results that are less stable and generalizable.

Second, in contrast to many previous studies that used high dosages of first-generation antipsychotics, usually haloperidol, creating an unfair comparison because of the increased risk of extrapyramidal symptoms and anticholinergic treatment, which may impair cognition,[51-54] this study used relative tablet strengths that were reviewed and approved by scientific experts and leaders from each of the pharmaceutical companies that manufacture the compounds. Further, the choice of perphenazine as the representative of the older antipsychotic medications may

have reduced the extrapyramidal symptoms and need for anticholinergic treatment associated with haloperidol and other high-potency first-generation antipsychotics,[63,82] especially since the dose range of 8 to 32 mg, equivalent to 2.5 to 10 mg of haloperidol, was lower than in most early studies.[83-85] Perphenazine, a phenothiazine, has been available since the late 1950s. It was selected for CATIE because it is a moderate-potency first-generation antipsychotic and causes only mild sedative effects and extrapyramidal symptoms in the dose range selected. Although it has never been considered to be an atypical antipsychotic, one of its metabolites, *N*-dealkylperphenazine, has relatively high affinity for serotonin 2A receptors, which by some definitions may confer atypical properties.[86] Therefore, prior studies may have documented, at least in part, negative effects associated with high-dose haloperidol treatment rather than an intrinsic, specific cognitive enhancement effect associated with some of the second-generation drugs vs the older medications. It will be important for health care professionals using perphenazine or other first-generation antipsychotics to carefully consider these dosage implications.

Third, compared with most clinical trials,[87] the present study had broad inclusion and minimal exclusion criteria and allowed comorbid conditions, concomitant medications, and current substance abuse. It was conducted at a variety of clinical settings where people with schizophrenia are treated. These "real-world" features of the study, which were intended to make the results more widely applicable,[87] may also account for the differences in results between this and previous studies. While single-site trials that are limited to research centers and highly screened patients may be more sensitive to the cognitive changes associated with treatment and may offer hope for the potential neurocognitive benefit of these medications, the current results may more accurately reflect clinical reality.

Fourth, at least 60% of patients in this study reported receiving atypical antipsychotic treatment prior to randomization, which is substantially higher than in many of the earlier studies, which were completed when treatment with second-generation antipsychotics was less common. However, only 16% of patients were randomized to the same drug they reported taking at baseline. Although the inclusion in our statistical analyses of patients' reports of their antipsychotic medication prior to randomization did not change the study results, it is possible that some of the potential neurocognitive benefit of the second-generation treatments examined in this study had already been realized prior to the initiation of the randomized treatment. If so, treatment effects may have been attenuated, but this would not explain the surprisingly beneficial effect of perphenazine.

Since the neurocognitive benefit of treatment in this study was small, the possibility that neurocognitive improvement was due solely to practice effects or expectation biases cannot be ruled out. In studies of antipsychotic medications, practice and placebo effects in schizophrenia are impossible to disentangle from treatment effects. However, 1 recent double-blind study comparing the effects of donepezil hydrochloride and placebo in a highly refined sample of 226 patients with schizophrenia stabilized while taking second-generation antipsychotics suggested that patients taking placebo who had negative symptom improvement also had neurocognitive effect size improvements of 0.22 SD after being tested twice over 6 weeks on the same test battery used in this study, suggesting a practice or placebo effect (R.S.E.K, Anil Malhotra, MD, H.Y.M., John Kane, MD, Robert Buchanan, MD, Anita Murthy, PharmD, Mindy Sovel, MA, Chunming Li, PhD, Robert Goldman, PhD, unpublished data, July 2004) consistent with the improvements reported herein. However, higher doses of haloperidol may blunt working memory performance[88] and procedural learning, likely mediators of practice-related performance improvements,[89,90] which may have conferred an advantage for the newer drugs in some previous studies, while patients treated with lower doses of haloperidol have demonstrated learning improvements, especially in first-episode samples.[10,91] Thus, while practice effects or expectation biases may be present in patients with schizophrenia on some tests, they may be adversely affected by certain treatments.

The elements of treatment compliance are complex,[92] and the current data support a weak relationship between neurocognitive improvement and treatment compliance because greater neurocognitive benefit was slightly associated with greater compliance. Although tenuous, these data may suggest either that increased compliance to treatment enhances cognitive benefit or that cognitive improvement encourages treatment compliance.[56]

Patients who had anticholinergic medication added during the first 2 months of treatment demonstrated no cognitive benefit, which was significantly less than those patients who did not have anticholinergics added. This result does not suggest that anticholinergic treatments should be withheld to aid cognition, however, since the extrapyramidal symptoms that are the targets of anticholinergic treatment are also associated with worse cognitive performance.[10,22]

In patients treated with quetiapine or ziprasidone, cognitive improvement predicted overall treatment effectiveness as measured by time to treatment discontinuation. These results suggest that treatment effectiveness is multiply determined and that cognitive improvement is one of the significant determinants. Cognitive change was a predictor of treatment discontinuation in patients receiving quetiapine and ziprasidone, which produced relatively weak symptom response in this study.[63] The differences between treatment groups in the contribution of cognitive improvement to longer periods to discontinuation suggest that cognitive improvement may be a contributor to treatment continuation in patients who are not demonstrating other symptom improvement or that the absence of cognitive improvement (or worsening) may be particularly important in the decision to discontinue treatment. Conversely, neurocognitive change may be a less important contributor to treatment continuation if symptom reduction is substantial. Finally, the amount of cognitive improvement that confers to improved functional outcomes such as quality of life is unknown. The various contributors to treatment discontinuation and quality of life in the CATIE trial will be evaluated comprehensively in a future report.

Several design features in this study limit the interpretation of the findings. First, the patient population in this study did not include patients with schizoaffective disorder, those with only 1 schizophrenic episode, or those who had adverse reactions to any of the treatments or were treatment resistant and was unlikely to include patients who had responded well to their current treatment. Thus, although this trial likely included a population that was more generalizable than most clinical trials,[87] this group of patients was still selective compared with the entire population of patients treated with antipsychotic medications, and the results must be viewed in this context. Second, a disadvantage to the random assignment of medications in this study is that if a medication is more effective for certain subgroups of patients who are recognizable by health care professionals, the effectiveness of this treatment will be reduced. Third, the randomization scheme prevented patients with TD from receiving treatment with perphenazine. Although all comparisons between perphenazine and the other treatments eliminated patients with TD, this differential screening process may still have given an advantage to perphenazine with regard to neurocognitive efficacy. The randomization of patients with TD, who may be less responsive to first-generation antipsychotic treatment,[93,94] may have inadvertently assigned to the perphenazine group patients who were more likely to respond to the only first-generation antipsychotic in the study. Finally, while the design of the CATIE trial allowed inclusion of patients not usually studied in clinical trials, only 817 (56%) of the 1460 patients in the trial generated neurocognitive data at baseline and after having received treatment with the same antipsychotic for 2 months, and only 303 patients (21%) generated neurocognitive data after having been treated with the same antipsychotic for 18 months. Furthermore, because of the differential discontinuation rate between the treatments,[63] a smaller percentage of patients were tested at end point with some of the treatments. Thus, the generalizability of these findings to the large community of patients receiving antipsychotics must be considered.

In sum, neurocognitive improvement associated with antipsychotic treatment in patients with schizophrenia was small and not different between treatments, including the first-generation antipsychotic perphenazine. A variety of issues may explain the contrast between the current findings and previous studies that had suggested an advantage of second-generation treatments, such as the relatively low dose of perphenazine, the overall high discontinuation rate in the study, and the lower percentage of patients entering the study while taking first-generation antipsychotics compared with earlier studies. Neurocognitive changes may be important predictors of treatment discontinuation with certain antipsychotics.

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REFERENCES

1. Saykin AJ, Gur RC, Gur RE, Mozley PD, Mozley LH, Resnick SM, Kester DB, Stafiniak P. Neuropsychological function in schizophrenia: selective impairment in memory and learning. *Arch Gen Psychiatry*. 1991;48:618-624.
2. Braff DL, Heaton R, Kuck J, Cullum M, Moranville J, Grant I, Zisook S. The generalized pattern of neuropsychological deficits in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting Test results. *Arch Gen Psychiatry*. 1991;48:891-898.
3. Brickman AM, Paul RH, Cohen RA, Williams LM, MacGregor KL, Jefferson AL, Tate DF, Gunstad J, Gordon E. Category and letter verbal fluency across the adult lifespan: relationship to EEG theta power. *Arch Clin Neuropsychol*. 2005;20:561-573.
4. Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P, Gur RC. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Arch Gen Psychiatry*. 1994;51:124-131.
5. Davidson M, Reichenberg A, Rabinowitz J, Weiser M, Kaplan Z, Mark M. Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. *Am J Psychiatry*. 1999;156:1328-1335.
6. Reichenberg A, Weiser M, Rapp MA, Rabinowitz J, Caspi A, Schmeidler J, Knobler HY, Lubin G, Nahon D, Harvey PD, Davidson M. Elaboration on premorbid intellectual performance in schizophrenia: premorbid intellectual decline and risk for schizophrenia. *Arch Gen Psychiatry*. 2005;62:1297-1304.
7. Fuller R, Nopoulos P, Arndt S, O'Leary D, Ho BC, Andreasen NC. Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. *Am J Psychiatry*. 2002;159:1183-1189.
8. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*. 1998;12:426-445.
9. Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, Pappadopulos E, Willson DF, Alvir JM, Woerner MG, Geisler S, Kane JM, Lieberman JA. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am J Psychiatry*. 2000;157:549-559.
10. Keefe RSE, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, Lewine RRJ, Yurgelun-Todd DA, Ruben CG, Tohen M, Tollefson GD, Sanger TM, Lieberman JA. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. *Am J Psychiatry*. 2004;161:985-995.
11. Gold JM, Queern C, Iannone VN, Buchanan RW. Repeatable battery for the assessment of neuropsychological status as a screening test in schizophrenia, I: sensitivity, reliability, and validity. *Am J Psychiatry*. 1999;156:1944-1950.
12. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry*. 1996;153:321-330.
13. Harvey PD, Howanitz E, Parrella M, White L, Davidson M, Mohs RC, Hoblyn J, Davis KL. Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: a comparison across treatment sites. *Am J Psychiatry*. 1998;155:1080-1086.
14. Hyman SE, Fenton WS. Medicine: what are the right targets for psychopharmacology? *Science*. 2003;299:350-351.
15. Keefe RSE, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, Rock SL, Woolson S, Tohen M, Tollefson GD, Sanger TM, Lieberman JA. Two-year neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. *Biol Psychiatry*. 2006;59:97-105.
16. Kern RS, Green MF, Marshall BD Jr, Wirshing WC, Wirshing D, McGurk SR, Marder SR, Mintz J. Risperidone vs. haloperidol on reaction time, manual dexterity, and motor learning in treatment-resistant schizophrenia patients. *Biol Psychiatry*. 1998;44:726-732.
17. Kivircik Akdede BB, Alptekin K, Kitis A, Arkar H, Akvardar Y. Effects of quetiapine on cognitive functions in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29:233-238.
18. Wagner M, Quednow BB, Westheide J, Schlaepfer TE, Maier W, Kuhn K. Cognitive improvement in schizophrenic patients does not require a serotonergic mechanism: randomized controlled trial of olanzapine vs. amisulpride. *Neuropsychopharmacology*. 2005;30:381-390.
19. McGurk SR, Carter C, Goldman R, Green MF, Marder SR, Xie H, Schooler NR, Kane JM. The effects of clozapine and risperidone on spatial working memory in schizophrenia. *Am J Psychiatry*. 2005;162:1013-1016.
20. Harvey PD, Meltzer H, Simpson GM, Potkin SG, Loebel A, Siu C, Romano SJ. Improvements in cognitive function following a switch to ziprasidone from conventional antipsychotics, olanzapine, or risperidone in outpatients with schizophrenia. *Schizophr Res*. 2004;66:101-113.
21. McGurk SR, Lee MA, Jayathilake K, Meltzer H. Cognitive effects of olanzapine treatment in schizophrenia. *MedGenMed*. 2004;6:27.

22. Harvey PD, Green MF, McGurk SR, Meltzer HY. Changes in cognitive functioning with risperidone and olanzapine treatment: a large-scale, double-blind, randomized study. *Psychopharmacology (Berl)*. 2003;169:404-411.
23. Harvey PD, Napolitano JA, Mao L, Gharabawi G. Comparative effects of risperidone and olanzapine on cognition in elderly patients with schizophrenia or schizoaffective disorder. *Int J Geriatr Psychiatry*. 2003;18:820-829.
24. Harvey PD, Siu CO, Romano S. Randomized, controlled, double-blind, multicenter comparison of the cognitive effects of ziprasidone versus olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Psychopharmacology (Berl)*. 2004;172:324-332.
25. Stip E, Remington GJ, Dursun SM, Reiss JP, Rotstein E, MacEwan GW, Chokka PR, Jones B, Dickson RAA. Canadian multicenter trial assessing memory and executive functions in patients with schizophrenia spectrum disorders treated with olanzapine. *J Clin Psychopharmacol*. 2003;23:400-404.
26. Sharma T, Hughes C, Soni W, Kumari V. Cognitive effects of olanzapine and clozapine treatment in chronic schizophrenia. *Psychopharmacology (Berl)*. 2003; 169:398-403.
27. Velligan DI, Prihoda TJ, Sui D, Ritch JL, Maples N, Miller AL. The effectiveness of quetiapine versus conventional antipsychotics in improving cognitive and functional outcomes in standard treatment settings. *J Clin Psychiatry*. 2003;64: 524-531.
28. Bilder RM, Goldman RS, Volavka J, Czobor P, Hoptman M, Sheitman B, Lindenmayer JP, Citrome L, McEvoy J, Kunz M, Chakos M, Cooper TB, Horowitz TL, Lieberman JA. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2002;159:1018-1028.
29. Good KP, Kiss I, Buiteman C, Woodley H, Rui Q, Whitehorn D, Kopala L. Improvement in cognitive functioning in patients with first-episode psychosis during treatment with quetiapine: an interim analysis. *Br J Psychiatry Suppl*. 2002; 43:s45-s49.
30. Vaiva G, Thomas P, Llorca PM, Dupont S, Cottencin O, Devos P, Mazas O, Rascle C, Steinling M, Goudemand M. SPECT imaging, clinical features, and cognition before and after low doses of amisulpride in schizophrenic patients with the deficit syndrome. *Psychiatry Res*. 2002;115:37-48.
31. Velligan DI, Newcomer J, Pultz J, Csernansky J, Hoff AL, Mahurin R, Miller AL. Does cognitive function improve with quetiapine in comparison to haloperidol? *Schizophr Res*. 2002;53:239-248.
32. Chua L, Chong SA, Pang E, Ng VPY, Chan YH. The effect of risperidone on cognitive functioning in a sample of Asian patients with schizophrenia in Singapore. *Singapore Med J*. 2001;42:243-246.
33. Fleming K, Thyrum P, Yeh C, Vargo DL, Potkin SG. Cognitive improvement in psychotic subjects treated with "Seroquel" (quetiapine fumarate): an exploratory study. *J Clin Psychopharmacol*. 2001;21:527-529.
34. Potkin SG, Fleming K, Jin Y, Gulasekaram B. Clozapine enhances neurocognition and clinical symptomatology more than standard neuroleptics. *J Clin Psychopharmacol*. 2001;21:479-483.
35. Purdon SE, Labelle A, Boulay L. Neuropsychological change in schizophrenia after 6 weeks of clozapine. *Schizophr Res*. 2001;48:57-67.
36. Purdon SE, Malla A, Labelle A, Lit W. Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. *J Psychiatry Neurosci*. 2001;26:137-149.
37. Smith RC, Infante M, Singh A, Khandat A. The effects of olanzapine on neurocognitive functioning in medication-refractory schizophrenia. *Int J Neuropsychopharmacol*. 2001;4:239-250.
38. Purdon SE, Jones BDW, Stip E, Labelle A, Addington D, David S, Breier A, Tollefson GD. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, and haloperidol. *Arch Gen Psychiatry*. 2000;57:249-258.
39. Lee MA, Jayathilake K, Meltzer HY. A comparison of the effect of clozapine with typical neuroleptics on cognitive function on neuroleptic responsive schizophrenia. *Schizophr Res*. 1999;37:1-11.
40. Galletly CA, Clark CR, McFarlane AC, Weber DL. Effects of clozapine for non-treatment-resistant patients with schizophrenia. *Psychiatr Serv*. 1999;50:101-103.
41. Kern RS, Green MF, Barringer MD Jr, Wirshing WC, Wirshing D, McGurk SR, Marder SR, Mintz J. Risperidone versus haloperidol on secondary memory: can newer medications air learning? *Schizophr Bull*. 1999;25:223-232.
42. Manschreck TC, Redmond DA, Candela SF, Maher BA. Effects of clozapine on psychiatric symptoms, cognition, and functional outcome in schizophrenia. *J Neuropsychiatry Clin Neurosci*. 1999;11:481-489.
43. Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull*. 1999;25:233-255.
44. Rossi A, Mancini F, Stratta P, Mattei P, Gismondi R, Pozzi F, Casacchia M. Risperidone, negative symptoms and cognitive deficit in schizophrenia: an open study. *Acta Psychiatr Scand*. 1997;95:40-43.
45. Serper MR, Chou JCY. Novel neuroleptics improve attentional functioning in schizophrenia patients: ziprasidone and aripiprazole. *CNS Spectr*. 1997;2:56-59.
46. Fujii DE, Ahmed I, Jokumsen M, Compton JM. The effects of clozapine on cognitive functioning in treatment-resistant schizophrenic patients. *J Neuropsychiatry Clin Neurosci*. 1997;9:240-245.
47. Hoff AL, Faustman WO, Wieneke M, Espinoza S, Costa M, Wolkowitz O, Csernansky JC. The effects of clozapine on symptom reduction, neurocognitive function, and clinical management in treatment-refractory state hospital schizophrenic inpatients. *Neuropsychopharmacology*. 1996;15:361-369.
48. Lee MA, Thompson P, Meltzer H. Effects of clozapine on cognitive function in schizophrenia. *J Clin Psychiatry*. 1994;55:82-87.
49. Buchanan RW, Holstein C, Breier A. The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance. *Biol Psychiatry*. 1994;36:717-725.
50. Hagger C, Buckley P, Kenny JT, Freidman L, Ubogy D, Meltzer HY. Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. *Biol Psychiatry*. 1993;34:702-712.
51. Keefe RS, Silva SG, Perkins DO, Lieberman JA. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. *Schizophr Bull*. 1999;25:201-222.
52. Harvey PD, Keefe RS. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am J Psychiatry*. 2001;158:176-184.
53. Woodward ND, Purdon SE, Meltzer HY, Zald DH. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *Int J Neuropsychopharmacol*. 2005;8:457-472.
54. Carpenter WT, Gold JM. Another view of therapy for cognition in schizophrenia. *Biol Psychiatry*. 2002;51:969-971.
55. Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *Am J Psychiatry*. 2006;163:185-194.
56. Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. *Schizophr Res*. 2002;57:209-219.
57. Stroup TS, McEvoy JP, Swartz MS, Byerly MJ, Glick ID, Canive JM, McGee MF, Simpson GM, Stevens MC, Lieberman JA. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. *Schizophr Bull*. 2003;29:15-31.
58. Keefe RS, Mohs RC, Bilder RM, Harvey PD, Green MF, Meltzer HY, Gold JM, Sano M. Neurocognitive assessment in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project schizophrenia trial: development, methodology, and rationale. *Schizophr Bull*. 2003;29:45-55.
59. Keefe RSE, Bilder RM, Harvey PD, Davis SM, Palmer BW, Gold JM, Meltzer HY, Green MF, Miller DD, Canive JM, Adler LW, Manschreck TC, Swartz M, Rosenheck R, Perkins DO, Walker TM, Stroup TS, McEvoy JP, Lieberman JA. Baseline neurocognitive deficits in the CATIE Schizophrenia Trial. *Neuropsychopharmacology*. 2006;31:2033-2046.
60. Swartz MS, Perkins DO, Stroup TS, McEvoy JP, Nieri JM, Haak DC. Assessing clinical and functional outcomes in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial. *Schizophr Bull*. 2003;29:33-43.
61. Davis SM, Koch GG, Davis CE, LaVange LM. Statistical approaches to effectiveness measurement and outcome-driven re-randomizations in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies. *Schizophr Bull*. 2003;29:73-80.
62. Rosenheck R, Doyle J, Leslie D, Fontana A. Changing environments and alternative perspectives in evaluating the cost-effectiveness of new antipsychotic drugs. *Schizophr Bull*. 2003;29:81-93.
63. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209-1223.
64. Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Rosenheck RA, Perkins DO, Keefe RSE, Davis CE, Severe J, Hsiao JK; the CATIE Investigators. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia after discontinuing a previous atypical antipsychotic. *Am J Psychiatry*. 2006;163:611-622.
65. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Rosenheck RA, Swartz MS, Perkins DO, Keefe RSE, Davis CE, Severe J, Hsiao JK; CATIE Investigators. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry*. 2006;163:600-610.
66. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophr Bull*. 1987;13:261-276.

67. Jastak S, Wilkinson GS. *Wide Range Achievement Test–Revised 3*. Wilmington, Del: Jastak Associates; 1993.
68. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988;75:800-803.
69. Guy W. *ECDEU Assessment Manual*. Rockville, Md: USDHEW; 1976.
70. Tracy K, Adler LA, Rotrosen J, Edson R, Lavori P. Interrater reliability issues in multicenter trials, part I: theoretical concepts and operational procedures in Department of Veterans Administration Cooperative Study #394. *Psychopharmacol Bull*. 1997;33:53-57.
71. IMS Health. Atypical antipsychotics—generating evidence to inform policy and practice. http://research.imshealth.com/research/research_schizophrenia.htm. Accessed August 26, 2005.
72. Faries D, Ascher-Svanum H, Zhu B, Correll C, Kane J. Antipsychotic monotherapy and polypharmacy in the naturalistic treatment of schizophrenia with atypical antipsychotics. *BMC Psychiatry*. 2005;5:26.
73. Benton AL, Hamscher K. *Multilingual Aphasia Examination Manual. Revised*. Iowa City: University of Iowa; 1978.
74. Wechsler D. *Wechsler Intelligence Scale for Children*. 3rd ed. Orlando, Fla: Harcourt Publishers; 1991.
75. Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR. Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Arch Gen Psychiatry*. 1997;54:159-165.
76. Brandt J, Benedict R. *Hopkins Verbal Learning Test*. Lutz, Fla: Psychological Assessment Resources; 1991.
77. Wechsler D. *Wechsler Adult Intelligence Scale*. Revised Edition. San Antonio, Tex: Psychological Corp; 1974.
78. Lafayette Instrument Company. *Grooved Pegboard Instruction Manual, Model 32025*. Lafayette, Ind: Lafayette Instrument Co; 1989.
79. Cornblatt BA, Keilp JG. Impaired attention, genetics, and the pathophysiology of schizophrenia. *Schizophr Bull*. 1994;20:31-46.
80. Lyons-Warren A, Lillie R, Hershey T. Short and long-term spatial delayed response performance across the lifespan. *Dev Neuropsychol*. 2004;26:661-678.
81. Kongs SK, Thompson LL, Iverson GL, Heaton RK. *Wisconsin Card Sorting Test—64 Card Version Professional Manual*. Odessa, Fla: Psychological Assessment Resources, Inc; 2000.
82. Rosenheck RA. Open forum: effectiveness versus efficacy of second-generation antipsychotics. haloperidol without anticholinergics as a comparator. *Psychiatr Serv*. 2005;56:85-92.
83. Høyberg OJ, Fensbo C, Remvig J, Lingjaerde O, Sloth-Nielsen M, Salvesen I. Risperidone versus perphenazine in the treatment of chronic schizophrenic patients with acute exacerbations. *Acta Psychiatr Scand*. 1993;88:395-402.
84. Fruensgaard K, Wollenberg J, Hansen KM, Fensbo C, Sihm F. Loxapine versus perphenazine in psychotic patients: a double-blind, randomized, multicentre trial. *Curr Med Res Opin*. 1978;5:601-607.
85. Van Putten T, Marder SR, Wirshing WC, Aravagiri M, Chabert N. Neuroleptic plasma levels. *Schizophr Bull*. 1991;17:197-216.
86. Sweet RA, Pollock BG, Mulsant BH, Rosen J, Sorisio D, Kirshner M, Henteleff R, DeMichele MA. Pharmacologic profile of perphenazine's metabolites. *J Clin Psychopharmacol*. 2000;20:181-187.
87. Haro JM, Edgell ET, Jones PB, Alonso J, Gavart S, Gregor KJ, Wright P, Knapp M; SOHO Study Group. The European Schizophrenia Outpatient Health Outcomes (SOHO) study: rationale, methods and recruitment. *Acta Psychiatr Scand*. 2003;107:222-232.
88. Castner SA, Williams GV, Goldman-Rakic PS. Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. *Science*. 2000;287:2020-2022.
89. Robbins TW. The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. *Psychopharmacology (Berl)*. 2002;163:362-380.
90. Harvey PD, Moriarty PJ, Serper MR, Schnur E, Lieber D. Practice-related improvement in information processing with novel antipsychotic treatment. *Schizophr Res*. 2000;46:139-148.
91. Harvey PD, Rabinowitz J, Eerdekens M, Davidson M. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. *Am J Psychiatry*. 2005;162:1888-1895.
92. Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: empirical and clinical findings. *Schizophr Bull*. 1997;23:637-651.
93. Chakos MH, Alvir JM, Woerner MG, Koreen A, Geisler S, Mayerhoff D, Sobel S, Kane JM, Borenstein M, Lieberman JA. Incidence and correlates of tardive dyskinesia in first episode of schizophrenia. *Arch Gen Psychiatry*. 1996;53:313-319.
94. Lieberman JA, Koreen AR, Chakos M, Sheitman B, Woerner M, Alvir JM, Bilder R. Factors influencing treatment response and outcome of first-episode schizophrenia: implications for understanding the pathophysiology of schizophrenia. *J Clin Psychiatry*. 1996;57(suppl 9):5-9.