Ziprasidone and Cognition: The Evolving Story

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Cognitive impairment, a central characteristic of schizophrenia, can profoundly limit patients' ability to acquire or maintain skills needed for adequate functioning. Thus, research on the efficacy of antipsychotic medications is increasingly focusing on the possible benefits of these agents on cognitive function. Although data are limited, it appears that atypical antipsychotics consistently improve cognitive function to a greater extent than do older, conventional agents. This review focuses on the atypical agent ziprasidone and its effects on cognitive function. The most recent data on the cognitive effects of ziprasidone come from a comparative trial with olanzapine (40–80 mg b.i.d. and 5–15 mg q.d., respectively) and from 3 studies in which patients were switched to ziprasidone (40–160 mg/day) because of suboptimal efficacy or tolerability with other antipsychotics. In general, ziprasidone-treated patients demonstrated significant improvements in multiple cognitive domains—such as episodic memory, attention/vigilance, executive function, and visuomotor speed—that are generally associated with improved functional outcome. In the switching studies, path analysis indicated that improvement on the Positive and Negative Syndrome Scale (PANSS) cognitive subscale directly affected changes on the PANSS anxiety–depression cluster and a PANSS "prosocial" subscale composed of items related to social engagement. Improvement in cognitive function observed with ziprasidone may have implications for long-term patient outcomes.

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Measures of cognitive function are increasingly being incorporated into clinical trials of antipsychotic medications as an important efficacy variable.[1] Cognitive impairment, a cardinal manifestation of schizophrenia, includes deficits in executive function, working memory, verbal fluency, attention/vigilance, and verbal and visual episodic learning and delayed recall memory. Such deficits may profoundly limit the ability of patients with schizophrenia to acquire, retain, or relearn skills necessary for real-world functioning.[2] Studies have shown that cognitive impairment contributes significantly to functional impairment.[3,4] A meta-analysis of 37 studies by Green and colleagues[5] confirmed that 4 neurocognitive constructs—secondary verbal memory, immediate verbal memory, executive function as measured by card sorting, and vigilance—were significantly associated with various aspects of functional outcome. Composite scores of cognitive performance, such as summary scores on neuropsychologic assessment batteries, have been reported to account for as much as 60% of the variance in measures of outcome status, even when the influence of other potential predictors such as negative symptoms is considered.[6]

Conventional antipsychotic medications have established efficacy in ameliorating psychotic symptoms in a substantial proportion of patients with schizophrenia, without substantially improving functional outcome.[7] Their efficacy in improving cognitive function is clearly less impressive.[8,9] Conversely, clinical trials examining the cognition enhancing effects of atypical antipsychotic medications, using a variety of methodologies, indicate that clozapine, risperidone, olanzapine, and ziprasidone all exert some beneficial effects on cognition.[1,5,10–13] A meta-analysis of 15 studies suggested that atypical antipsychotics are more effective than conventional agents in improving results on measures of cognitive function in patients with schizophrenia.[8]

OVERVIEW OF PHARMACOLOGIC PROFILES

It is beyond the scope of this article to describe in detail the pharmacologic differences between conventional and atypical agents. Some differences are briefly noted, however, because they have been hypothesized to explain the differences in effects on cognitive function across these classes of agents.

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Table 1. Cognitive Battery Tests Used in Clinical Trials of Ziprasidone[a]

Domain	Importance in Schizophrenia	Tests Administered
Learning/memory	Predicts community outcome/daily activities, psychosocial skills acquisition, and social problem solving	RAVLT Spatial Working Memory Test
Attention/vigilance	Important for educational/occupational functions and activities of daily living Predicts social problem solving and skills acquisition, deficits of which are associated with poor outcome	TMT part A (also tests motor skills) DSDT CPT
Executive function	Predicts community outcome/daily activities	TMT part B (also tests motor skills) WCST
Visuomotor speed	Predicts community outcome/daily activities	TMT parts A and B
Verbal fluency	Predicts community outcome/daily activities	Category Fluency Test Letter Fluency Test

[a]Adapted from Harvey et al.[27]
Abbreviations: CPT = Continuous Performance Test, DSDT = Digit Span Distraction Test, RAVLT = Rey Auditory Verbal Learning Test, TMT = Trail-Making Test, WCST = Wisconsin Card Sorting Test.

All atypical antipsychotic agents are more potent blockers of serotonin-2A (5-HT_{2A}) receptors than of dopamine-2 (D_2) receptors.[14] Although dopamine activity is abnormal in persons with schizophrenia, other neurotransmitters, including 5-HT, are most likely involved in the pathology of the illness.[15] Agents that are antagonists at 5-HT_{2A} receptors (i.e., atypical antipsychotics) may be more beneficial in improving cognitive function than agents that predominantly block D_2 receptors (i.e., conventional antipsychotics).[16,17] Cortical dopamine release associated with 5-HT_{2A} antagonism is hypothesized to be a critical factor in cognitive improvement associated with novel antipsychotic treatment.[13] All $5\text{-HT}_{2A}/D_2$ antagonists also increase release in the prefrontal cortex of acetylcholine, another neurotransmitter that is implicated in cognitive dysfunction in many illnesses, such as Alzheimer's disease, and may be important in schizophrenia as well.[18]

The atypical antipsychotic ziprasidone has a unique pharmacologic profile characterized by a very high affinity for the 5-HT_{2A} receptor, high affinity for the D_2 receptor, and negligible affinity for muscarinic M_1 receptors.[19] Furthermore, ziprasidone displays a high affinity for 5-HT_{1A} (where it is a partial agonist), 5-HT_{1D}, and 5-HT_{2C} receptors. Agonism of 5-HT_{1A} may also contribute to the increased release of cortical dopamine.[14] A study of anesthetized rats by Sprouse and colleagues[20] showed that the 5-HT_{1A} agonism of ziprasidone is key to its inhibitory effect on the firing of serotonergic neurons in the dorsal raphe nucleus.[20] Ziprasidone has only modest α_1-adrenergic and histaminergic activity and is a moderately potent blocker of both serotonin and norepinephrine reuptake into synaptic terminals.[19,21]

ZIPRASIDONE AND COGNITIVE FUNCTION: CLINICAL TRIAL DATA

Short- and long-term clinical trials of ziprasidone have established its efficacy against positive, negative, and affective symptoms.[22–26] Because of the emerging evidence of the link between cognitive function and patient outcomes, recent clinical trials of ziprasidone have also incorporated a battery of cognitive measures, including tests of learning/memory, attention/vigilance, executive function, visuomotor speed, and verbal fluency (Table 1). Findings indicating that ziprasidone may improve cognitive function in patients with schizophrenia have come from 3 open-label switch studies[28,29] and a 6-week comparative trial (with a 6-month continuation) versus olanzapine.[27,32]

Table 2. PANSS Subscales Used in Ziprasidone Switch Studies[a]

PANSS cognitive subscale
- N5: Difficulty in abstract thinking
- N7: Stereotyped thinking
- G4: Tension
- G5: Mannerisms and posturing
- G11: Poor attention
- G12: Lack of judgment and insight

PANSS anxiety–depression cluster[30]
- G1: Somatic concern
- G2: Anxiety
- G3: Guilt feelings
- G6: Depression
- G15: Preoccupation

PANSS prosocial subscale[31]
- G16: Active social avoidance
- N4: Passive social withdrawal
- N2: Emotional withdrawal
- P6: Suspiciousness/persecution
- N7: Stereotyped thinking
- P3: Hallucinatory behavior

[a]Adapted from Lindenmayer et al.[30] and Purnine et al.[31]
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Switch Studies

The effects of ziprasidone on cognitive function were assessed in 3 identically designed 6-week, multicenter, open-label, parallel-group switch studies.[28,29] Enrollees comprised 270 patients (200 men, 70 women) between 18 and 55 years of age with stable symptomatic schizophrenia or schizoaffective disorder. All were switched from conventional antipsychotic drugs (N = 108), olanzapine (N = 104), or risperidone (N = 58) because of suboptimal efficacy or tolerability. The switch to ziprasidone was

Table 3. Change in Cognitive Battery Assessments After Switching to Ziprasidone From Other Antipsychotics[a]

	Switched From Conventionals		Switched From Olanzapine		Switched From Risperidone	
Test	Mean (SE) Change	Effect Size	Mean (SE) Change	Effect Size	Mean (SE) Change	Effect Size
RAVLT						
Total learning	2.9 (0.866)**	0.26	4.5 (0.951)***	0.39	3.9 (1.374)**	0.32
Long-delay recall	1.1 (0.321)***	0.29	1.3 (0.287)***	0.34	1.4 (0.302)***	0.37
Recognition/discrimination	0.03 (0.014)**	0.31	0.04 (0.010)***	0.36	0.04 (0.017)*	0.33
Spatial Working Memory						
5-s delay	–1.2 (0.930)	0.28	0.3 (0.818)	0.06	1.8 (1.057)	0.21
15-s delay	–0.09 (0.668)	0.02	0.4 (0.553)	0.08	0.7 (0.620)	0.11
DSDT	5.4 (2.466)*	0.23	2.1 (2.169)	0.10	4.4 (1.960)*	0.22
TMT						
Part A	–6.6 (2.674)*	0.21	–0.2 (1.941)	0.01	–1.0 (1.946)	0.06
Part B	–18.6 (6.098)**	0.23	0.5 (4.709)	0.00	–6.8 (5.314)	0.12
WCST						
Categories attained	–0.2 (0.198)	0.09	0.3 (0.165)	0.09	0.8 (0.268)**	0.34
Total errors	–0.7 (2.545)	0.02	–3.1 (2.092)	0.12	–9.7 (2.557)***	0.35
Category Fluency Test	1.3 (1.263)	0.12	1.6 (0.735)*	0.12	0.6 (0.972)	0.04
Letter Fluency Test	2.7 (0.873)**	0.24	0.3 (0.807)	0.02	2.4 (1.060)*	0.21

[a]Data from Harvey et al.[28]
*p < .05.
**p < .01.
***p < .001.
Abbreviations: DSDT = Digit Span Distraction Test, RAVLT = Rey Auditory Verbal Learning Test, TMT = Trail-Making Test, WCST = Wisconsin Card Sorting Test.

accomplished using 1 of 3 randomly assigned strategies: abrupt discontinuation, slow taper, or fast taper. Regardless of switch strategy, all patients were receiving ziprasidone alone at the end of week 1. The dosage of ziprasidone was 40 mg b.i.d. for the first 2 days, after which it ranged between 40 and 160 mg/day divided into 2 doses through week 6 or early discontinuation. Anticholinergics and benzodiazepines were permitted as needed but were not allowed 12 hours before cognitive testing.

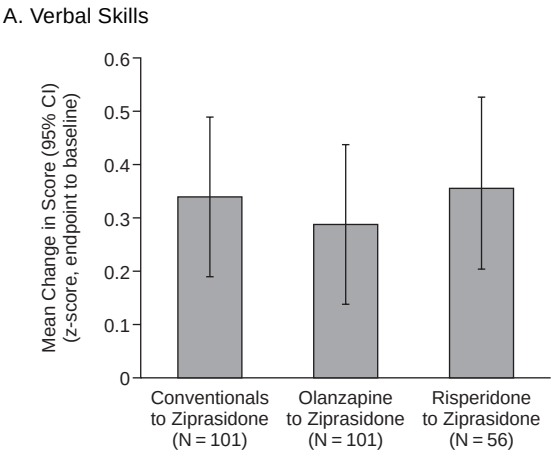
At baseline (randomization) and 6 weeks of treatment (endpoint), patients were evaluated with tests of learning/memory (Rey Auditory Verbal Learning Test [RAVLT], Spatial Working Memory Test), attention/vigilance (Trail-Making Test [TMT] part A, Digit Span Distraction Test [DSDT], Continuous Performance Test [CPT]), executive function (TMT part B, Wisconsin Card Sorting Test [WCST]), and verbal fluency (Category Fluency Test, Letter Fluency Test) (Table 1). Additional measures (Table 2)[30,31] included the Positive and Negative Syndrome Scale (PANSS) cognitive subscale, as well as measures of affective symptoms (the PANSS anxiety–depression cluster of Lindenmayer et al.[30]) and of changes in social engagement using a subscale of the PANSS based on a "prosocial" factor.[31]

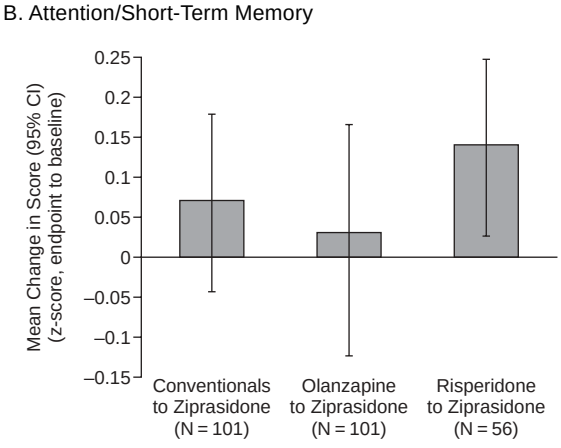
Mean changes from baseline to endpoint (week 6 or early discontinuation) were analyzed by paired t test using the last observation carried forward in all patients. Statistical significance was determined by 2-sided paired t tests.[28,29] The effect size (Cohen's d) was calculated by dividing the mean change from baseline by the standard deviation based on the pooled baseline scores across all 3 switch groups. Principal components factor analysis was performed to test for clustering of cognitive battery variables. Path analysis was used to explore the direct and indirect effects of the change in PANSS cognitive score on the change in PANSS prosocial score. The potential mediating effects of changes in PANSS anxiety–depression scores on PANSS prosocial scores were also explored.

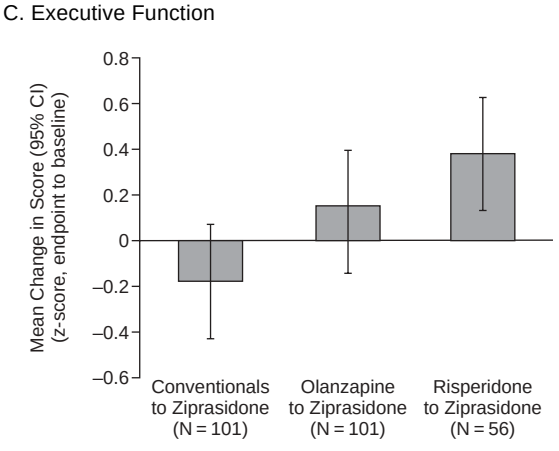
Patients switched to ziprasidone from conventional agents, olanzapine, or risperidone demonstrated significant improvement in test scores in the cognitive battery, although not every test score improved in all studies (Table 3).[28] No significant decline in a test score occurred in any study. Using factor analysis, 18 cognitive variables were reduced to 3 domains: verbal skills, attention/short-term memory, and executive function. Analysis of z-transformed mean change in factor scores showed that verbal skills improved significantly following the switch from conventional agents, olanzapine, or risperidone (Figure 1A). Attention/short-term memory also improved across studies, although significance was reached only in the group switched from risperidone (Figure 1B). Executive function also improved significantly in the group switched from risperidone (Figure 1C). A global cognitive measure showed significant improvements in patients switched to ziprasidone from conventional agents, olanzapine, or risperidone (Figure 2).

PANSS cognitive subscale scores improved significantly in patients switched to ziprasidone from conventional agents ($p < .05$) and risperidone ($p < .001$).[28] Patients switched from olanzapine also improved, but the change was not significant. Similarly, the PANSS anxiety–depression cluster scores demonstrated significant improvement in patients switched to ziprasidone from con-

Figure 1. Changes in (A) Verbal Skills, (B) Attention/Short-Term Memory, and (C) Executive Function in Patients Switched to Ziprasidone From Other Antipsychotics[a]

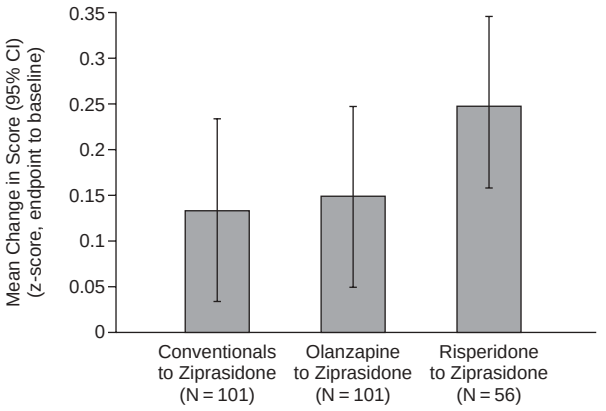






[a]Data from Harvey et al.[28] Mean ziprasidone dosages for study completers were 91.2 mg/day, 90.0 mg/day, and 92.0 mg/day for patients switched from conventionals, olanzapine, and risperidone, respectively.
Abbreviation: CI = confidence interval.

Figure 2. Change in Global Cognitive Scores From Baseline to Endpoint in Patients Switched to Ziprasidone From Other Antipsychotics[a]



[a]Data from Harvey et al.[28] Mean ziprasidone dosages for study completers were 91.2 mg/day, 90.0 mg/day, and 92.0 mg/day for patients switched from conventionals, olanzapine, and risperidone, respectively.
Abbreviation: CI = confidence interval.

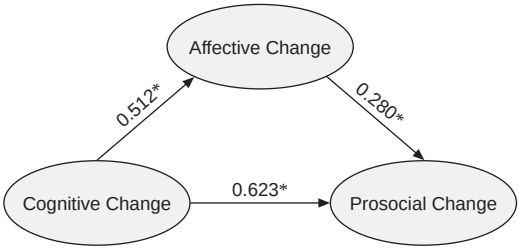
ventional agents and risperidone ($p < .005$ for both), whereas the improvement seen in those switched from olanzapine was not statistically significant. Patients in all 3 studies showed significant improvement in social engagement and behaviors as evaluated by the PANSS prosocial subscale ($p < .05$ in patients switched from conventional agents and olanzapine, $p < .001$ in patients switched from risperidone).

Path analysis of each switch study revealed similar interrelations between cognitive, affective, and prosocial outcomes.[28] Using pooled data from the 3 studies (N = 258), path analysis suggested that improvement in PANSS cognitive subscale score directly affected PANSS prosocial improvement (path coefficient, 0.623; $p < .001$) (Figure 3). Improvement in PANSS cognitive subscale score also directly affected PANSS anxiety–depression cluster (path coefficient, 0.512; $p < .001$), and through this measure had an indirect effect on PANSS prosocial improvement (path coefficient, $0.512 \times 0.280 = 0.143$). The total effect of cognitive subscale improvements on prosocial improvement equaled the sum of both the direct and indirect effects ($0.623 + 0.143 = 0.766$ [$p = .001$, unadjusted effect]). Improvement in PANSS anxiety–depression cluster score had a direct effect on PANSS prosocial improvement (path coefficient, 0.280; $p < .001$).

Ziprasidone Versus Olanzapine

Cognitive data from a 6-week trial. Additional data concerning the cognitive effects of ziprasidone were derived from a 6-week, multicenter, double-blind, parallel-designed trial comparing ziprasidone with olanzapine.[27,32] The 269 enrolled patients (176 men and 93 women; age

Figure 3. Relation of Cognitive and Affective Improvements With Prosocial Change After Switch to Ziprasidone in 3 Switch Studies: Path Analysis (PANSS subscales, N = 258)[a]



[a]Data from Harvey et al.[28] Results shown are path coefficients. Mean ziprasidone dosages for study completers were 91.2 mg/day, 90.0 mg/day, and 92.0 mg/day for patients switched from conventionals, olanzapine, and risperidone, respectively.
*p < .001.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

range, 18 to 55 years) were hospitalized with a history of persistent psychotic symptoms for at least a week before admission to the study. At screening and baseline, all had scores ≥ 4 on the Clinical Global Impressions-Severity of Illness scale and on ≥ 1 of the following positive symptoms in the PANSS: delusions, conceptual disorganization, or hallucinatory behavior. Patients were randomized 1:1 to ziprasidone (N = 136) or olanzapine (N = 133) treatment. Ziprasidone dosage was 40 mg b.i.d. on days 1 and 2; 80 mg b.i.d. on days 3 to 7; and 40, 60, or 80 mg b.i.d. during weeks 2 to 6. Olanzapine was given in a dosage of 5 mg q.d. on days 1 and 2; 10 mg q.d. on days 3 to 7; and 5, 10, or 15 mg q.d. during weeks 2 to 6. Concomitant administration of lorazepam and benztropine was permitted.

The battery of cognitive tests performed at baseline (1 day after withdrawal of previous medication) and at 6 weeks of treatment (or endpoint) included measures of attention/vigilance, executive function, learning/memory, and verbal fluency, as described above (Table 1).[27,32] The PANSS was also administered. Antipsychotics, lorazepam, and benztropine were withheld, if possible, 12 hours before scheduled cognitive tests.

Changes in scores from baseline were evaluated in patients who completed the study and tested against the null hypothesis of no significant change in either treatment group using 2-tailed t tests.[27,32] Statistical tests were performed at a 5% 2-tailed significance level. Effect size (Cohen's d) was calculated by dividing mean change by standard deviation. Analysis of between-group differences in score changes was performed with multivariate analysis of variance (MANOVA) on all cognitive variables.

At endpoint, significant improvements from baseline for both ziprasidone- and olanzapine-treated patients were noted in attention ($p < .01$ and $p < .001$, respectively), visuomotor speed ($p < .01$ and $p < .05$, respectively), executive function ($p < .05$ and $p < .001$, respectively), and learning/memory ($p < .001$ for both) (Table 4).[27] Neither treatment group demonstrated significant improvements on DSDT, WCST, or Letter Fluency.

For ziprasidone-treated patients, improvement in PANSS positive scores was correlated with improvement in DSDT nondistraction (memory domain; $r = 0.35$, $p < .05$) and with WCST categories attained (executive function; $r = –0.38$, $p < .05$).[27,32] For olanzapine-treated patients, greater improvement in PANSS positive scores was correlated with improvements in RAVLT discrimination (memory domain; $r = –0.39$, $p < .01$), WCST categories attained (executive function; $r = –0.29$, $p < .05$), and Category Fluency (verbal fluency; $r = –0.30$, $p < .05$). Improvement in PANSS negative scores was correlated with greater improvement in DSDT distraction (memory domain; $r = –0.35$, $p < .05$) in ziprasidone-treated patients and with improvements in CPT d' total score (attention domain; $r = –0.31$, $p < .05$); WCST categories attained (executive function; $r = –0.31$, $p < .05$); and Category Fluency (verbal fluency; $r = –0.38$, $p < .01$). MANOVA of baseline-to-endpoint changes in scores for all cognitive variables revealed no statistically significant difference between ziprasidone and olanzapine.

Cognitive data from a 6-month continuation trial. Additional assessments of cognitive function were obtained during a 6-month continuation study, which enrolled 126 patients who responded satisfactorily to ziprasidone or olanzapine in the 6-week trial.[33] Significant (within-group) mean improvements were seen with ziprasidone (N range, 23–33) and olanzapine (N range, 22–35) in all domains. Ziprasidone was associated with larger effect sizes for cognitive improvement than olanzapine on most of the variables. This included TMT part A (–32.64 vs.–10.17; effect size [ES], 0.60 vs. 0.63; $p \leq .004$ for both), RAVLT sum 1 to 5 (11.67 vs. 7.77; ES, 0.97 vs. 0.70; $p < .001$ for both), Delayed Recall (3.58 vs. 2.15; ES, 1.06 vs. 0.72; $p < .001$ for both), WCST perseverative errors (–9.09 vs.–3.68; ES, 0.66 vs. 0.33; $p = .004$ vs. $p = .14$), and Letter Fluency (4.06 vs. 3.53; ES, 0.64 vs. 0.36; $p < .001$ vs. $p = .04$). Olanzapine showed larger effect sizes than ziprasidone on TMT part B (–49.48 vs. –42.67; ES, 0.97 vs. 0.61; $p < .0001$ vs. $p = .002$), Category Fluency (4.32 vs. 0.58; ES, 0.09 vs. 0.56; $p = .002$ vs. $p = .618$), and CPT d' (0.40 vs. 0.33; ES, 0.63 vs. 0.5; $p = .002$ vs. $p = .01$). MANOVA revealed no significant difference in cognitive performance between groups.

DISCUSSION

In the 3 switch studies reviewed, patients whose prior antipsychotic therapy was suboptimal with respect to effectiveness or tolerability experienced improved cognitive function when switched to ziprasidone (40–160

Table 4. Change From Baseline to Endpoint on Measures of Cognitive Function in Patients Treated With Ziprasidone or Olanzapine[a]

	Ziprasidone				Olanzapine			
		Change				Change		
Measure	N	Mean	SD	Effect Size	N	Mean	SD	Effect Size
Attention/vigilance								
CPT d' total	43	0.262**	0.624	0.420	55	0.328***	0.646	0.507
DSDT								
Distraction/nondistraction	55	–3.688	18.935	0.195	68	–2.164	16.539	0.131
Nondistraction	55	–1.558	16.318	0.096	68	0.315	20.971	0.015
Visuomotor speed								
TMT part A	55	–16.709**	40.884	0.409	69	–6.924*	25.621	0.271
Executive function								
TMT part B	58	–17.345*	55.018	0.315	77	–28.623***	60.863	0.470
WCST								
Categories attained	52	–0.038	1.782	0.022	69	0.435	1.736	0.250
Perseverative errors	45	–2.533	12.749	0.199	59	–1.678	14.197	0.118
Learning/memory								
RAVLT trials 1–5 (sum)	62	4.919***	9.921	0.496	79	6.494***	8.286	0.784
Verbal fluency								
Category Fluency Test	62	–0.016	8.829	0.002	77	2.130*	7.142	0.298
Letter Fluency Test	60	0.483	7.053	0.069	77	0.468	8.859	0.053

[a]Data from Harvey et al.[27]
*p < .05.
**p < .01.
***p < .001.
Abbreviations: CPT d' = Continuous Performance Test (attention domain), DSDT = Digit Span Distraction Test, RAVLT = Rey Auditory Verbal Learning Test, TMT = Trail-Making Test, WCST = Wisconsin Card Sorting Test.

mg/day), as indicated by improvements in scores on the PANSS cognitive subscale, individual tests in a cognitive battery, and 3 factors (verbal skill, attention/short-term memory, and executive function) identified through factor analysis. Improvement in affective symptoms, particularly in patients switched from conventional antipsychotics or risperidone, was observed in these studies, as was improved social engagement and behaviors, as evaluated by the PANSS prosocial subscale. Path analysis of pooled data suggests that improvements in cognitive and affective symptom clusters mediated improvement in PANSS prosocial score. Improvement on the PANSS cognitive subscale also contributed to observed change in affective symptoms. The observed interrelation in improvement in cognition function, affective symptoms, and social engagement is an intriguing focus for future investigation.

Ziprasidone appears to be as effective at enhancing cognition in clinically unstable patients with schizophrenia as olanzapine, a medication that has been reported to have beneficial effects on cognitive function in this population.[9] In the 6-week comparative trial, both ziprasidone (40–80 mg b.i.d.) and olanzapine (5–15 mg b.i.d.) were associated with significantly improved measures of verbal memory, vigilance, aspects of motor speed, and executive function. The effect sizes observed with ziprasidone were similar to those reported with atypical agents in similar nonrefractory patients.[1] Although the mean change for some variables was approximately 0.5 SD, some patients clearly derived substantial benefit. In addition, the magnitude of change noted for ziprasidone in variables where the improvement was statistically significant was consistent with that reported for both olanzapine and risperidone in a previous clinical trial of similar nonrefractory patients. Notably, after 6 months, patients receiving ziprasidone and olanzapine continued to demonstrate improvements in attention/vigilance, learning/memory, executive function, and verbal fluency, with more pronounced benefits observed in those receiving ziprasidone. Perhaps possible differences among atypicals may be further demonstrated over time.

Collectively, the results of these studies suggest that ziprasidone enhances a wide range of cognitive domains in patients with stable and unstable schizophrenia. The domains in which ziprasidone-treated patients exhibited improved performance—episodic memory, attention/vigilance, executive function, and visuomotor speed—are among those that have been repeatedly shown to be associated with important aspects of functional outcome, such as social-skill acquisition and employment.[6] Improvement in specific domains of cognitive function may improve social, functional, and adaptive outcomes in patients with schizophrenia. Thus, the improvement in cognitive function observed with ziprasidone may have implications for long-term patient outcomes.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril and others), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal), ziprasidone (Geodon).

REFERENCES

1. Harvey PD, Keefe RSE. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am J Psychiatry 2001;158:176–184

2. Green MJ. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996;153:321–330
3. Friedman JI, Harvey PD, McGurk SR, et al. Correlates of change in functional status in institutionalized geriatric schizophrenic patients: focus on medical comorbidity. Am J Psychiatry 2002;159:1388–1394
4. Velligan DI, Mahurin RK, Diamond PL, et al. The functional significance of symptomatology and cognitive function in schizophrenia. Schizophr Res 1997;25:21–31
5. Green MF, Marshall BD Jr, Wirshing WC, et al. Does risperidone improve verbal working memory in treatment resistant schizophrenia? Am J Psychiatry 1997;154:799–804
6. Green MF, Kern RS, Braff DL, et al. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull 2000;26:119–136
7. Hegarty JD, Baldessarini RJ, Tohen M, et al. One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am J Psychiatry 1994;151:1409–1416
8. Keefe RSE, Silva SG, Perkins DO, et al. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. Schizophr Bull 1999;25:201–222
9. Bilder RM, Goldman RS, Volavka J, et al. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 2002;159: 1018–1028
10. Hagger C, Buckley P, Kenny JT, et al. Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. Biol Psychiatry 1993;34:702–712
11. Potkin SG, Fleming K, Jin Y, et al. Clozapine enhances neurocognition and clinical symptomatology more than standard neuroleptics. J Clin Psychopharmacol 2001;21:479–483
12. Purdon SE. Cognitive improvement in schizophrenia with novel antipsychotic medications. Schizophr Res Suppl 1999;35:S51–S60
13. Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr Bull 1999;25:233–255
14. Ichikawa J, Ishii H, Bonaccorso S, et al. 5-HT_{2A} and D_2 receptor blockade increases cortical DA release via 5-HT_{1A} receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. J Neurochem 2001;76:1521–1531
15. Davis KL, Kahn RS, Ko G, et al. Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry 1991;148: 1474–1486
16. Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin$_2$ pK_i values. J Pharmacol Exp Ther 1989;251:238–246
17. Weinberger DR, Gallhofer B. Cognitive function in schizophrenia. Int Clin Psychopharmacol 1997;12(suppl 4):S29–S36
18. Ichikawa J, Dai J, O'Laughlin IA, et al. Atypical, but not typical, antipsychotic drugs increase cortical acetylcholine release without an effect in the nucleus accumbens or striatum. Neuropsychopharmacology 2002;26: 325–339
19. Schmidt AW, Lebel LA, Howard HR Jr. Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. Eur J Pharmacol 2001;425:197–201
20. Sprouse JS, Reynolds LS, Braselton JP, et al. Comparison of the novel antipsychotic ziprasidone with clozapine and olanzapine: inhibition of dorsal raphe cell firing and the role of 5-HT_{1A} receptor activation. Neuropsychopharmacology 1999;21:622–631
21. Seeger TF, Seymour PA, Schmidt AW, et al. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J Pharmacol Exp Ther 1995;275:101–113
22. Daniel DG, Zimbroff DL, Potkin SG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Neuropsychopharmacology 1999;20:491–505
23. Keck P Jr, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. Psychopharmacology (Berl) 1998;140:173–184
24. Goff DC, Posever T, Herz L, et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 1998;18: 296–304
25. Hirsch S, Kissling W, Bauml J, et al. A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. J Clin Psychiatry 2002;63:516–523
26. Arató M, O'Connor R, Meltzer HY, et al. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. Int Clin Psychopharmacol 2002;17:207–215
27. Harvey PD, Simpson GM, Loebel A, et al. Ziprasidone vs olanzapine for cognitive function in schizophrenia [poster]. Presented at the Sixth Biannual Mt. Sinai Conference on Cognition in Schizophrenia; March 28–29, 2003; Colorado Springs, Colo
28. Harvey PD, Loebel A, Siu CO, et al. Cognitive, affective, and prosocial improvement after switch to ziprasidone [poster]. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
29. Harvey PD, Meltzer HY, Simpson GM, et al. Improvement in cognitive function following a switch to ziprasidone from conventional antipsychotics, olanzapine, or risperidone in outpatients with schizophrenia. Schizophr Res. In press
30. Lindenmayer JP, Bernstein-Hyman R, Grochowski S. A new five factor model of schizophrenia. Psychiatr Q 1994;65:299–322
31. Purnine DM, Carey KB, Maisto SA, et al. Assessing positive and negative symptoms in outpatients with schizophrenia and mood disorders. J Nerv Ment Dis 2000;188:653–661
32. Harvey PD, Siu C, 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) 2003 Nov 13 [Epub ahead of print]
33. Harvey PD, Siu CO, Romano S. Ziprasidone vs olanzapine in schizophrenia: 6-month cognitive data. Presented at the 55th Institute on Psychiatric Services; Oct 29–Nov 2, 2003; Boston, Mass