Changes in Neurocognitive Function in Patients With Schizophrenia After Starting or Switching to Amisulpride in Comparison With the Normal Controls

Yong Min Ahn, MD, PhD, Kyu Young Lee, MD, PhD,† Chul-Eung Kim, MD, PhD,‡ Jae-Jin Kim, MD, PhD,§ Dae-Yeob Kang, MD, PhD,|| Tae-Youn Jun, MD, PhD,¶ Jin Sook Choi, MD, PhD,# In-Won Chung, MD, PhD,** Se Hyun Kim, MD,* Samuel S.-H. Hwang, MA,* and Yong Sik Kim, MD, PhD**

Abstract: We examined short- and long-term changes in neurocognitive functions in patients with schizophrenia who were either started or switched to amisulpride in comparison with the normal controls. Fifty-seven patients treated with amisulpride and 60 normal controls completed a comprehensive neurocognitive function test battery at the baseline, the 8-week, and the 1-year follow-up. We conducted and compared the results of both intention-to-treat (ITT) and per-protocol (PP) analyses to account for the follow-up loss. Three general results obtained were as follows: (1) the degree of the improvements in neurocognitive function was comparable to those of other second-generation antipsychotics in both ITT and PP analysis; (2) in light of the relative effect size, the composite effect size and the effect size in most measures in both ITT and PP analyses were smaller for the patient group than those of the control group, signifying that improvement in performance may be largely attributable to practice effects; and (3) nonetheless, there were evidences of both short- and long-term improvements in some cognitive tasks, such as in the Korean-Wechsler Adult Intelligence Scale vocabulary subtest and the Trail Making Test, that may not be accounted by practice effect. These results suggest the need to include a healthy control group to validate the medication effect of cognitive improvements in patients with schizophrenia and to consider practice effect in interpreting the results of repeated administration of neurocognitive function tests.

Key Words: amisulpride, schizophrenia patients, neurocognitive function, healthy control, practice effect

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From the *Department of Psychiatry and Behavioral Science and Institute of Human Behavioral Medicine, Seoul National University College of Medicine, Seoul National University Hospital; †Department of Neuropsychiatry, Eulji University School of Medicine, Eulji General Hospital, Seoul; ‡Department of Psychiatry, Inha University College Medicine, Incheon; §Department of Psychiatry and Diagnostic Radiology, Yonsei University College of Medicine, Yongong Severance Hospital, Seoul; ||Department of Psychiatry, Yong-In Mental Hospital, Yong-In; ¶Department of Psychiatry, St. Mary's Hospital, The Catholic University; #Department of Psychiatry, Seoul Medical Center, Seoul; and **Department of Psychiatry, Dongguk University College of Medicine, Dongguk Unversity International Hospital, Gyeonggi-do, Korea.

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Reprints: Yong Sik Kim, MD, PhD, Department of Psychiatry and Behavioral Science and Institute of Human Behavioral Medicine, Seoul National University College of Medicine, Seoul National University Hospital, 28 Yongon-Dong, Chongno-Gu, Seoul, 110-744, Korea (e-mail: kys@snu.ac.kr).

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Although the mechanisms underlying the effectiveness of the "second-generation" antipsychotics (SGAs) have not been fully elucidated to date,[1–3] many advantages of their use over the "first-generation" antipsychotics (FGAs) have been reported, including better treatment efficacy in negative symptoms of schizophrenia[4] and reduced extrapyramidal side effects.[5] Evidences further lend strong support for better neurocognitive outcome with SGAs compared with FGAs,[1,6,7] which directly translates into improvement in social and occupational functioning[8] and quality of life[9] for patients with schizophrenia. However, studies comparing various SGAs[10,11] as well as a meta-analysis of studies comparing SGAs with FGAs[6] have not found improvements in all cognitive domains but rather selective improvements that differed according to the type of SGAs used.

Amisulpride can be distinguished from other SGAs in that, unlike those with high affinity for dopamine (D_2) and serotonin ($5HT_{2A}$) receptors, such as risperidone and ziprasidone, or for a broad range of central receptors, such as clozapine, olanzapine, zotepine, and quetiapine, it is a selective D_2 and D_3 receptor antagonist[12] devoid of any affinity for D_1, adrenergic, cholinergic, and serotonergic receptors.[13] The results of comparison studies with other SGAs thus far have yielded that the patients taking amisulpride performed as well as those on high D_2-$5HT_{2A}$ affinity antipsychotics in some cognitive domains, such as working memory, or even better in others, such as executive function,[11] sustained attention and social functioning and auditory short-term memory and visuospatial recognition memory.[2,3]

Despite evidences supporting the efficacy of amisulpride in improving cognitive function, there has been an apparent lack of well-designed research on this topic. For one, the studies that have examined the cognitive effect of amisulpride have invariably involved comparison with other SGAs[11] or FGAs[14] or in combination with quetiapine,[2,3] without including normal healthy controls. This may present critical limitations in interpreting the results because such a design does not preclude the possibility that observed cognitive improvements may be due to what is collectively known as practice effects rather than medication, as Goldberg et al[15] have argued. They compared the neurocognitive performances of patients with schizophrenia taking either risperidone or olanzapine with those of a healthy control group at the baseline and after 6 and 16 weeks and concluded that with the exceptions of memory for visual designs and trail making, the "magnitude of the [treatment] effect is in keeping with a practice-related phenomenon."

Another problem commonly shared by such studies is that they often did not cover both short- and long-term cognitive changes. Most studies, in fact, have examined relatively short-term effect of medication, mostly ranging from 8 to 12 weeks, and some studies, such as that by Wagner et al,[11] have identified positive changes in some domains of cognitive function.

However, it is also necessary to examine the effect of amisulpride on cognitive function over an extended period, as evidence suggests that significant changes in negative symptoms may occur as late as 12 months.[16] As an exception, Tyson et al[2] have made follow-up assessments at 9 and 18 months after baseline and reported more benefits of using quetiapine and amisulpride in digit span and visuospatial memory. However, they found the direction of the changes to be almost completely identical for both assessment periods, whereby it could be argued that their results do not sufficiently account for the short-term cognitive changes.

In the present study, we have examined the short-term (baseline to week 8) and the long-term (week 8 to year 1) changes in neurocognitive function in patients with schizophrenia after starting or switching to amisulpride. There is a lack of consensus on whether the cognitive deficits in patients with schizophrenia are isolated or global in nature,[17] and, accordingly, we have designed a neurocognitive test battery to cover a range of neurocognitive domains that have been frequently examined in similar studies. Lastly, by including a healthy normal control group, we examined which of the improvements, if any, may be attributable to the effect of amisulpride after controlling for practice effect.

METHODS

Participants

Korean in- or outpatients, aged 18 to 65 years, satisfying the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnostic criteria of either schizophrenia or schizophreniform disorder were eligible for this multicenter study. These subjects had either newly developed or recurrent psychosis after discontinuation of antipsychotics or needed a switch in their antipsychotic medication due to side effects, insufficient treatment effectiveness, and/or other reasons. Exclusion criteria included patients with psychotic disorder other than schizophrenia or schizophreniform disorder, patients having medical problems contraindicated to amisulpride such as prolactin-dependent tumor, pheochromocytoma, hypersensitivity to metabolites of amisulpride, severe bradycardia, hyperkalemia, elongated QT interval, or significant abnormalities in electrocardiogram. Pregnant or breast-feeding women, patients having clinically significant medical or neurologic conditions, and those refractory to previous treatment (lack of effectiveness to more than 2 different types of antipsychotic agents for more than 8 weeks) were also excluded. Fifty-seven patients and 60 normal participants matched according to age and sex as a control group were included in this study.

The written informed consent was obtained from all participants before any study procedure, and this study was approved by the institutional review board of the respective center.

Treatments of Amisulpride and Other Interventions

The investigators in this study were allowed to determine the dose of amisulpride based on their clinical decisions (50–1200 mg/d) to follow real clinical practice, although they had been recommended to use high dose (400–800 mg/d, maximum to 1200 mg/d) for the positive symptoms and low dose (50–300 mg/d) for the negative symptoms. In case where the patient was taking other antipsychotic agent, concomitant medication with amisulpride was allowed only for the first week of trial. Benzodiazepines (diazepam, oxazepam, and lorazepam), zolpidem, zopiclone, antiparkinson drugs, and other drugs were allowed only when necessary to treat anxiety, behavior problems, insomnia, and extrapyramidal symptoms. Other psychotropic medications such as antipsychotic agents, antidepressants or mood stabilizers, and levodopa were not permitted during the study.

Neurocognitive Function Assessment

A comprehensive test battery was designed to cover a range of neurocognitive domains, including general intelligence, working memory and executive function, verbal and nonverbal memory, attention, and psychomotor speed. It took approximately 90 to 120 minutes to complete the battery, which was well tolerated by both controls and patients, and all test procedures were carried out by a trained psychiatrist or a clinical psychologist blind to the hypotheses of the study.

The test battery was administered 3 times, at the baseline, the 8-week, and the 1-year follow-ups. For patients in acute stage, baseline data were obtained within 2 weeks of starting or switching to amisulpride to secure cooperation and reliable test performance.

The following entails the neurocognitive tests included in the battery:

General intelligence. We used the shortened version of the Korean-Wechsler Adult Intelligence Scale (K-WAIS),[18,19] which included digit span, vocabulary, arithmetic, picture arrangement, and block-design subtests. Among the measures, vocabulary, arithmetic, picture arrangement, and block-design subtests were used to derive the full-scaled IQ score.

Executive function and working memory. Executive function and working memory were measured by the Controlled Oral Word Association Test (COWAT) or letter fluency test, which assessed the ability of a person to think of words that begin with a specific letter[20] in a 1-minute period. Three trials were administered with 3 different letters, and the number of correct response and perseveration were obtained.[21]

Verbal and nonverbal memory function. Verbal and nonverbal memory functions were assessed by administering the Rey-Kim Memory Test,[22] consisting of the Auditory Verbal Learning Test (AVLT)[23] and the Rey's Complex Figure Test (RCFT).[24] The measures obtained from the AVLT were the sum of the words recalled in trials 1 to 5, delayed free recall (20 minutes) and delayed recognition, and from RCFT, copy, immediate, and delayed recall scores. The composite index of memory function (MQ) was derived from the combination of AVLT and RCFT measures.

Attention. The measures of attention were obtained by administering Conners' Continuous Performance Test (CPT) for Windows.[25] The measures assessed were omission errors, commission errors, mean reaction time, SE of reaction, and d'.

Psychomotor speed. Trail Making Tests A and B (TMT-A and TMT-B) were used to assess visuomotor speed and accuracy. The time required to complete trail A and trail B as well as the number of errors were recorded.

Data Analysis

All data were analyzed using the Statistical Package for the Social Sciences for Windows (version 12.0; SPSS Inc, Chicago, Ill). The main effect and the interaction between the patient group and the normal control group were analyzed using repeated-measures analysis of variance (ANOVA) with baseline, 8-week, and 1-year (end point) scores as the dependent

variables, time as a within-subject repeated measure, and treatment group (amisulpride and control) as a between-subjects fixed factor. Where a significant interaction was found, simple 1-way ANOVA was carried out to examine group × time interaction between the pairs of consecutive assessment points, followed by within-subjects contrast of 2 consecutive assessment points.

For those subjects who were lost to follow-up at 1 year (end point), we used the last-observation-carried-forward method to account for the lost data. There were 13 such cases for the patient group and 18 for the control group. No significant demographic differences were found between the lost-to-follow-up and the remaining group for both patient and control group. For comparison of results, both the intention-to-treat (ITT) analysis and the per-protocol (PP) analysis were presented.

Lastly, significance was set at $P < 0.004$ after Bonferroni correction for multiple comparisons (1-tailed test of $P > 0.10$ divided by 24 variables).

RESULTS

Demographic Data

In the ITT analysis, there were 33 males and 24 females in the patient group and 28 males and 32 females in the control group. Four were de novo patients starting amisulpride, and the remaining were switching patients. The mean age and the education level were 32.83 ± 7.79 and 12.53 ± 2.63 years, respectively, for the patient group and 32.7 ± 8.81 and 13.17 ± 2.41 years, respectively, for the control group. The Positive and Negative Syndrome Scale total scores were 78.77 ± 16.88, 62.16 ± 13.1, and 57.16 ± 15.41 for the baseline, the 8-week, and the 1-year follow-ups, respectively.

In the PP analysis, 25 males and 19 females remained for the patient group, and 18 males and 24 females remained for the control group. The patient group had the mean age of 32.89 ± 7.91 years with 12.36 ± 2.63 years of education, whereas the control group had the mean age of 31.45 ± 8.21 years with 13.03 ± 2.38 years of education. For both ITT and PP analyses, there were no statistical significances in sex distribution, age, and years of education.

Although patients with either schizophrenia or schizophreniform disorder were eligible, only those diagnosed as schizophrenia actually participated in this study. Among them, 35 (61.4%) were paranoid subtype, 1 (1.8%) was disorganized, 18 (31.6%) were undifferentiated, and 3 (5.3%) were residual.

As for the treatment dosage, the mean dose prescribed at baseline, 8 weeks, and 1 year were 284.21 ± 150.94, 489.47 ± 256.13, and 529.82 ± 301.02 mg for the ITT group, respectively, and 284.09 ± 144.58, 477.27 ± 229.12, and 529.55 ± 292.8 mg for the PP group, respectively. For concomitant medication, at the baseline, 28 patients (49.1%) did not take any benzodiazepines, 24 patients (42.1%) took lorazepam, and 5 patients (8.85%) took other medications, such as zolpidem and alprazolam. There were no baseline group differences between users and nonusers of benzodiazepine for demographic characteristics and all neurocognitive measures.

Neurocognitive Performance

Presented in Table 1 are the F and the P values of the ITT and the PP analysis for repeated ANOVA. The control group showed superior performance across all cognitive tasks ($P < 0.001$), and both groups show significant improvement in most cognitive performances over the 1-year follow-up period.

The Korean-Wechsler Adult Intelligence Scale

In the ITT analysis, as measured by the shortened version of K-WAIS, the performance on the block-design subtest significantly improved over the 1-year period for the patient group, which was attributable to a significant improvement during the first 8-week period ($F = 8.404$, $P = 0.004$). In the control group, the block-design subscales showed significant improvement over the 1-year period, with a significant change in the baseline versus the 8-week comparison ($F = 23.628$, $P = 0.0001$). No significant group × time interaction was found in the full-scaled IQ and in any of the subscales of K-WAIS.

The result of the PP analysis, however, showed the patient group to have marginally significant improvement over the 1-year period in the full-scaled IQ and the block design. On the other hand, the control group showed marginally significant improvement in the full-scaled IQ and significant improvement in the block design. Notably, group × time interaction for the vocabulary subtest approached but did not reach the level of significance, which was mostly attributable to the improvement in the score between the 8-week and the 1-year follow-up ($F = 4.569$, $P = 0.036$) for the patient group. No other notable interaction was found.

The Controlled Oral Word Association Test

As for COWAT, the ITT analysis revealed a significant increase in the number of correct response over a 1-year period for both the patient and the control group. Significant 8-week short-term improvement ($F = 12.853$, $P = 0.001$) was evident in the patient group and the control group. No significant change was observed during the same period in the number of perseverative response for the patient and the control group.

In the PP analysis, the number of correct responses also increased significantly for the patient group during the 1-year period, but the control group only showed marginally significant improvement during the same period. Further analysis using within-subjects simple contrast revealed a significant short-term improvement in the patient group between the baseline and the 8-week follow-up ($F = 10.010$, $P = 0.003$).

The Rey-Kim Memory Test

In ITT analysis, as measured by the performances on AVLT and RCFT, the full-scaled MQ increased significantly over the duration of the study for the patient group where significant improvement occurred between baseline and 8 weeks ($F = 19.980$, $P = 0.000$) and maintained thereafter. However, comparative improvement in performance was obtained from the control group as well, with significant improvement from baseline to 8 weeks ($F = 93.543$, $P = 0.000$).

In other measures of memory function, significant overall improvement over 1 year was observed for the patient group in AVLT sum of trials 1 to 5 and RCFT immediate recall and delayed recall. In addition, further analysis of simple contrasts between the assessment periods for all these measures yielded significant baseline to 8-week improvements (AVLT sum of trials 1–5, $F = 21.138$, $P = 0.000$; RCFT immediate recall $F = 22.682$, $P = 0.000$; RCFT delayed recall $F = 23.713$, $P = 0.000$). The control group also showed significant improvement in the same measures in the comparison of baseline and 8 weeks (AVLT sum of trials 1–5, $F = 145.56$, $P = 0.000$; AVLT delayed recall, $F = 65.58$, $P = 0.000$; RCFT immediate recall $F = 38.325$, $P = 0.000$; RCFT delayed recall $F = 42.791$, $P = 0.000$).

The analyses of group × time interactions yielded significant interaction in full-scaled MQ and AVLT sum of trials 1 to 5 and marginally significant interaction in AVLT

TABLE 1. *F* and *P* Values of Within-Groups Repeated ANOVA Over 1 Year in ITT and PP Analysis

	ITT Analysis						PP Analysis					
	Amisulpride, n = 57		Control, n = 60		Groups × Time Interaction		Amisulpride, n = 44		Control, n = 42		Groups × Time Interaction	
	F	*P*	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*
K-WAIS: general intelligence												
Full-scaled IQ	2.559	0.082	4.814	0.010	0.403	0.669	5.358	0.006	4.141	0.019	0.304	0.738
Digit span	1.782	0.173	4.981	0.008	0.191	0.826	1.616	0.205	3.090	0.051	0.210	0.807
Vocabulary	1.683	0.190	0.719	0.489	1.935	0.147	3.467	0.036	0.680	0.509	3.501	0.032
Arithmetic	0.007	0.993	0.258	0.773	0.097	0.908	0.304	0.738	0.127	0.881	0.014	0.986
Picture arrangement	1.088	0.340	5.547	0.005	2.301	0.102	1.503	0.228	2.755	0.069	1.441	0.240
Block design	5.866	0.004	14.176	0.000	0.701	0.497	5.228	0.007	9.931	0.000	0.525	0.593
COWAT: working memory and executive function												
Correct response	8.466	0.000	7.932	0.001	0.036	0.964	6.160	0.003	4.498	0.014	0.058	0.943
Perseveration	1.605	0.206	0.574	0.565	2.131	0.121	1.763	0.178	0.776	0.463	2.335	0.100
Rey-Kim Memory Test: verbal and nonverbal memory												
Full-scaled MQ	14.938	0.000	84.309	0.000	7.767	0.001	14.091	0.000	51.106	0.000	3.637	0.028
AVLT 1–5 sum	9.841	0.000	78.771	0.000	8.783	0.000	11.158	0.000	44.598	0.000	3.035	0.051
AVLT delayed recall	3.847	0.024	53.232	0.000	6.618	0.002	4.686	0.012	29.918	0.000	1.626	0.200
AVLT delayed recognition	0.25	0.779	2.350	0.100	0.804	0.449	0.375	0.689	1.558	0.217	0.521	0.595
Rey-Kim Memory Test: verbal and nonverbal memory												
RCFT copy	0.378	0.686	0.323	0.724	0.419	0.658	0.167	0.195	0.024	0.976	1.345	2.263
RCFT immediate	19.137	0.000	27.258	0.000	1.143	0.321	14.591	0.000	16.813	0.000	0.450	0.638
RCFT delayed	21.907	0.000	30.331	0.000	0.273	0.761	16.056	0.000	20.817	0.000	0.278	0.758
Conners' CPT: attention*												
Omission	0.623	0.538	1.422	0.245	0.13	0.878	0.894	0.413	3.089	0.051	0.495	0.484
Commission	4.542	0.013	2.470	0.089	0.992	0.372	1.229	0.298	2.432	0.094	0.167	0.684
Reaction time	0.525	0.593	0.203	0.816	0.598	0.551	0.475	0.624	0.103	0.903	0.269	0.605
SE of reaction	0.578	0.563	1.798	0.170	0.855	0.427	0.751	0.475	2.112	0.128	1.200	0.277
d′	1.226	0.298	1.640	0.198	1.227	0.295	0.590	0.557	2.495	0.089	0.395	0.531
TMT: psychomotor speed												
Trail A time	5.914	0.004	3.968	0.021	2.195	0.114	3.153	0.048	3.288	0.042	4.433	0.242
Trail A error	1.085	0.341	1.000	0.371	0.798	0.452	2.811	0.066	1.519	0.225	3.218	0.043
Trail B time	0.382	0.684	2.520	0.085	1.052	0.351	0.788	0.458	1.918	0.153	1.715	0.183
Trail B error	0.983	0.378	0.937	0.395	0.297	0.744	0.638	0.531	1.519	0.225	0.026	0.974

*Based on 41 patients and 42 controls for the PP analysis; 3 patients did not complete the test.

delayed recall. They were all accountable only by significant or marginally significant interaction in the baseline versus the 8-week comparison (full-scaled MQ, $F = 11.698$, $P = 0.000$; AVLT sum of trials 1 to 5 $F = 12.843$, $P = 0.000$; AVLT delayed recall, $F = 7.000$, $P = 0.009$), where greater improvement in performance was observed by the control group.

The results of the PP analysis closely followed that of ITT analysis: the full-scaled MQ increased significantly over the 1-year study period for both the patient and the control group, where significant improvement occurred between baseline and 8 weeks for both groups ($F = 20.260$, $P = 0.000$ and $F = 93.543$, $P = 0.000$, respectively, for the patient group and the controls). Other measures of memory function maintained their significance in the PP analysis for the patient group, including the AVLT sum of trials 1 to 5 and RCFT immediate recall and delayed recall, which were all attributable to significant baseline to 8-week improvement. Similarly, the control group also followed the results of the ITT analysis, whereby significant overall improvement in AVLT sum of trials 1 to 5, AVLT delayed recall, and RCFT immediate and delayed recall were all attributable to significant baseline to 8-week improvement.

The Continuous Performance Test

In the measures of attention as measured by the Conners' CPT II, the results of both ITT and PP analyses revealed no significant improvement in both the patient and the control groups. No group × time interaction was found in either ITT or PP analysis.

The Trail Making Tests A and B

Lastly, in psychomotor speed as measured by Trail Making Tests A and B, trail A time was significantly decreased only for the patient group over the year in the ITT analysis. No significant differences or interactions were found.

Consistent results were found in the PP analysis, where trail A time showed marginally significant decrease for the patient group. No statistically significant interaction was found.

Comparison of Effect Size

For the comparison of the performance between the patient and the control group, the relative effect size (Cohen *d*) for each variable is presented in Table 2. In the ITT analysis, the composite effect sizes of the baseline to week 8 and the week 8 to year 1 comparisons for the patient group were 0.16 and 0.01, respectively, and 0.25 and −0.03 for the control group, respectively. The PP analysis showed comparable results, where the composite effect sizes of the baseline to week 8 and the week 8 to year 1 comparisons for the patient group were 0.18 and 0.04, respectively, and 0.27 and −0.05 for the control group, respectively. Overall, the control group showed higher effect size than the patient group, with a few notable exceptions. Looking at only those variables that showed a consistent pattern across ITT and PP analyses, the patient group, in the baseline to week 8 comparison, showed larger effect size than the control group in the COWAT number of correct responses and TMT trail A number of errors. Likewise, in the week 8 to year 1 comparison, larger effect size was found for patients in K-WAIS vocabulary and block-design subtests, COWAT number of perseverative response, RCFT copy and immediate and delayed recall, Conners' CPT number of commission errors, reaction time, and *d′*, and TMT trail A time and trail B time. However, although many of the differences were small and ranged below 0.10, the patient group showed relatively superior short-term effect size than the control group in COWAT number of correct response and TMT trail A errors as well as superior long-term effect in K-WAIS vocabulary subtest, COWAT perseverative response, CPT reaction time sum and *d′*, and TMT trail A time and trail B time.

DISCUSSION

By including both ITT and PP analyses and healthy normal controls in our design, we have applied more strict standards to examining both short- and long-term cognitive effects of amisulpride. As the result, we have obtained the following 3 general results: (1) the degree of neurocognitive

TABLE 2. The Effect Sizes, or Cohen *d*, of the Baseline to Week 8 and the Week 8 to Year 1 Comparisons

	ITT Analysis				PP Analysis			
	Patient		Control		Patient		Control	
	Baseline to Week 8	Week 8 to Year 1	Baseline to Week 8	Week 8 to Year 1	Baseline to Week 8	Week 8 to Year 1	Baseline to Week 8	Week 8 to Year 1
K-WAIS: general intelligence								
Full-scaled IQ	0.08	0.08	0.16	0.01	0.18	0.11	0.19	0.02
Digit span	0.07	0.08	0.08	0.15	0.08	0.10	0.01	0.20
Vocabulary	−0.02	0.16	−0.07	−0.02	0.08	0.23	−0.08	−0.02
Arithmetic	0.00	0.00	0.05	0.00	0.06	0.01	0.04	0.00
Picture arrangement	0.10	−0.08	0.23	0.09	0.14	−0.09	0.17	0.14
Block design	0.17	0.01	0.32	−0.04	0.21	0.01	0.37	−0.06
COWAT: working memory and executive function								
Correct response	0.38	−0.02	0.27	0.01	0.41	−0.03	0.34	0.01
Perseverative response	0.17	−0.29	−0.04	0.15	0.17	−0.53	0.00	0.18
Rey-Kim Memory Test: verbal and nonverbal memory								
Full-scaled MQ	0.37	−0.02	0.88	−0.09	0.45	−0.02	0.84	−0.12
AVLT sum of trials 1 to 5 (words)	0.38	−0.15	0.95	−0.18	0.50	−0.20	0.97	−0.27
AVLT delayed recall	0.25	−0.12	0.72	−0.09	0.34	−0.15	0.64	−0.13
AVLT delayed recognition	0.07	−0.02	0.28	−0.08	0.10	−0.02	0.30	−0.10
Rey-Kim Memory Test: verbal and nonverbal memory								
RCFT copy	−0.02	0.10	−0.11	0.01	0.11	0.14	−0.04	0.04
RCFT immediate recall	0.39	0.06	0.59	0.00	0.41	0.09	0.58	0.00
RCFT delayed recall: 20 min	0.42	0.09	0.56	0.05	0.41	0.13	0.59	0.07
Conners' CPT: attention*								
Omission error	−0.05	−0.04	−0.11	−0.13	−0.06	−0.09	−0.15	−0.29
Commission error	−0.31	0.07	−0.20	0.12	−0.17	0.04	−0.26	0.17
Reaction time sum, ms	0.04	−0.07	−0.05	0.04	0.04	−0.09	−0.02	0.06
SE of reaction	−0.08	0.14	−0.13	−0.09	−0.02	0.13	−0.18	−0.11
d′	0.17	0.13	0.18	−0.14	0.03	0.11	0.28	−0.20
TMT: psychomotor speed								
Trail A time, s	−0.27	−0.12	−0.25	0.09	−0.18	−0.14	−0.32	0.15
Trail A error	−0.17	0.25	0.13	0.10	−0.44	0.24	0.24	0.15
Trail B time, s	−0.01	−0.07	−0.26	0.13	0.02	−0.13	−0.34	0.19
Trail B error	−0.21	0.17	−0.10	0.17	−0.17	0.15	−0.34	0.33

*Based on 41 patients and 42 controls for the PP analysis; 3 patients did not complete the test.

improvement by amisulpride was comparable to those obtained by other SGAs[2,3,11]; (2) the composite effect size and the effect size in most measures were smaller for the patient group than those of the control group, signifying that improvement in performance may be in fact attributable to what is collectively referred to practice effect; and (3) nonetheless, there are tentative evidences for both short- and long-term improvements in some specific cognitive tasks, such as in K-WAIS vocabulary subtest and TMT, that may not be accounted by practice effect alone.

Considering only the patient group, our results showed both short- and long-term improvement in a number of measures, some of which were consistent with previous studies.[2,3,11] However, in light of the performance of the control group, it became strongly suggestive that the improvement may largely reflect practice or exposure effect. For one, the composite short-term effect size (baseline to week 8 comparison) of the patient group (ITT = 0.16, PP = 0.18) was much smaller than the control group (ITT = 0.25, PP = 0.27). Furthermore, the patient group also showed dramatic long-term (week 8 to year 1) decrease in effect size (ITT = 0.01, PP = 0.04). Such results parallel those obtained by Goldberg et al,[15] where the magnitude of the effect was greatest in the 0- to 6-week period than the 6- to 16-week period. As for the positive result obtained from K-WAIS vocabulary subtest, improvement in primary negative symptoms may have played a role,[14] as Gold et al,[26] in their 5-year longitudinal study, have found significant correlations between the changes in negative symptoms and verbal IQ and full-scale IQ. However, the lack of further research on this topic presents a limitation in interpreting such findings and in formulating hypotheses concerning the effect of amisulpride on the relationship between negative symptoms and specifically verbal functioning. Nonetheless, as vocabulary subtest has been found to provide a good estimate of premorbid IQ,[27] it may be worthwhile to replicate this finding to confirm the effect of amisulpride on verbal functioning and to examine how that relates to its action on negative symptoms. Needless to say, the same can be said of TMT-A speed and accuracy, which has been supported in part by Goldberg et al.[15]

The examination of the relative effect size also revealed superior short-term effect in COWAT number of correct response, Conners' CPT commission errors, and trail B errors as well as superior long-term effect in COWAT perseverative response and trail B time. It may be worthwhile to consider the cluster of measures where the patient group showed relatively superior effect size (>0.10) than the control group in short-term (ie, TMT-A errors) and/or long-term comparisons (ie, K-WAIS vocabulary subtest, COWAT perseverative response, CPT reaction time sum and d', and TMT-A time and TMT-B time). With exceptions of vocabulary and CPT reaction time, all these measures have been traditionally considered as measures of executive function. However, because these differences have not been substantiated by significant group × time interaction, such results should not be considered as a conclusive evidence of improvement.

We have examined the short- and the long-term cognitive effect of amisulpride using a repeated-measures multivariate analysis, which is believed by some authors (eg, Weiss et al[1]) to be the most appropriate analysis for such data. In addition, consistent with the study by Goldberg et al,[15] we have also included a healthy control group in our study. However, unlike their study design, which included the baseline to 16-week (end point) comparison, we did not include the baseline to end point comparison in our design because our primary concern was to separately examine the effect of medication during the acute stage (the short-term, baseline to week 8 comparison) and the maintenance stage (the long-term, week 8 to year 1 comparison). Nonetheless, a separate analysis revealed that the pattern of cognitive improvement from the baseline to the end point was quite consistent with our overall results with only COWAT correct response, full-scaled MQ, RCFT immediate and delayed recall, and TMT-A time showing significant or marginally significant improvement.

The results of this study are mostly in line with the conclusion drawn by Goldberg et al[15] and demonstrate the need to account for practice effects in designing studies that measure efficacy of antipsychotic medication in relation to cognitive functioning. There is a clear possibility of new learning and memory over repeated trials confounding the observation of improvement,[1] and verbal memory, in particular, has been found to be strongly sensitive to practice effect over repeated trial.[28] Hence, future investigations should be designed with a keen awareness of the susceptibility of the cognitive tasks to practice effects and use caution when selecting neurocognitive measures for their study design. A number of methods have been used by various researchers to avoid possible practice effects, including identifying the learning "plateau" before measuring cognitive effect of intervention,[29,30] using alternative forms (eg, Woods et al,[31] Beglinger et al,[32] and Shapiro and Harrison[33]), and in some cases, counterbalancing,[34] but many of the tasks were not still completely free from certain aspects of practice effects, such procedural learning.[32] Therefore, future efforts should be placed on examining how the performance on various cognitive function tests may be subject to practice effects and how to control them. On the other hand, in the absence of alternative forms for repeated administrations, the comparisons with the control group may prove useful in identifying particular domains of cognitive improvement in patients with schizophrenia with the use of a particular antipsychotic medication. Although recruitment of a comparative normal control group may present difficulty especially in long-term longitudinal studies, efforts should be made to include them in the future study designs to account for the practice effects and to better define the unique patterns of cognitive effects associated with antipsychotic medications.

AUTHOR DISCLOSURE INFORMATION

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