Neurocognitive Effectiveness of Haloperidol, Risperidone, and Olanzapine in First-Episode Psychosis: A Randomized, Controlled 1-Year Follow-Up Comparison

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Objective: To investigate the neurocognitive effectiveness of haloperidol, risperidone, and olanzapine in first-episode schizophrenia-spectrum disorders.

Method: This prospective, randomized, open-label study was conducted from February 2001 to February 2005. Data for the present investigation were obtained from a large epidemiologic and 3-year longitudinal intervention program of first-episode psychosis (DSM-IV criteria) conducted at the outpatient clinic and the inpatient unit at the University Hospital Marques de Valdecilla, Santander, Spain. One hundred four patients randomly assigned to haloperidol (N = 35), olanzapine (N = 30), or risperidone (N = 39) who completed clinical and cognitive evaluations at baseline, 6 months, and 1 year were included in the final analysis. Thirty-seven healthy individuals were also longitudinally assessed. A neuropsychological battery that comprised 9 cognitive domains was used. The contribution of clinical changes, concomitant medications, and the severity of motor side effects to cognitive changes was controlled. The main outcome measure was cognitive changes at 1-year follow-up.

Results: The 3 treatment groups showed a significant improvement in cognitive scores after 1 year. The differential cognitive effectiveness between antipsychotics was insignificant. The magnitude of cognitive changes was similar in the 3 treatment groups and controls, although a greater improvement on the Finger Tapping Test, Trail Making Test B, and Rey Complex Figure Test was found in the treatment groups. Clinical changes, use of concomitant medications, and the emergence of motor side effects did not significantly account for cognitive changes over time.

Conclusions: Haloperidol, olanzapine, and risperidone were equally effective in treating cognitive deficits of psychosis. The effect of practice clearly contributes to cognitive score improvements after treatment with antipsychotics. Our results provide important information regarding the practical utility of antipsychotic treatments to improve cognition and could have implications for developing novel approaches for cognitive pharmacotherapy in schizophrenia.

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The improvement of cognitive impairments has come to be viewed as a fundamental objective of clinical trials in schizophrenia. The initial clinical trials on chronic samples had suggested that there was a beneficial effect of second-generation antipsychotics (SGAs) on neurocognitive deficits compared to first-generation antipsychotics (FGAs).[1,2] The presence of relevant confounders associated with chronicity might bias these findings. Thus, longitudinal studies of first-episode schizophrenia patients are of special relevance to evaluate the effect of antipsychotics on cognition.

Previous studies in first-episode schizophrenia have drawn conflicting conclusions. Keefe and colleagues[3]

demonstrated in a 12-week follow-up study that olanzapine produced significantly more cognitive benefit than haloperidol. Interestingly, in the same sample, no differences were found at lengthy (1-year and 2-year) follow-up evaluations between treatments.[4] Cognitive effectiveness of risperidone and haloperidol was also examined in a sample of early psychosis patients who had almost all been exposed to neuroleptic.[5] At 3 months, risperidone was significantly more beneficial than haloperidol on general cognitive function and verbal fluency and long-delay free recall. Consistently, 2 other studies have also reported a greater improvement with risperidone relative to haloperidol in the short term.[6,7] Purdon et al.[8] found a greater cognitive benefit with olanzapine relative to haloperidol and risperidone. In a recent article, Goldberg and colleagues[9] described similar cognitive score improvements with risperidone and olanzapine after 4 months. The cognitive changes found in patients were consistent in magnitude with the practice effects observed in controls. It is of note that haloperidol seems to distinctively produce a greater interference with practice effect.[10]

Critically, the use of low doses of FGAs, to set up lengthy follow-up studies, the assessment of practice effect, and to lessen the rate of dropouts are methodological issues that need to be addressed in order to shed new light on the cognitive effectiveness of antipsychotics. Our aim was to investigate the cognitive effects of haloperidol, risperidone, and olanzapine in first-episode psychosis. Our results herein are not subject to most of the previous concerns, and the strengths of our research are (1) a large representative sample of drug-naive patients, (2) the inclusion of a control group to assess practice effect, (3) the use of low doses of haloperidol, (4) 1-year follow-up, (5) low dropout rate, and (6) no industry sponsorship of the study.

METHOD

Study Setting and Financial Support

Data for the present investigation were obtained from a large epidemiologic and 3-year longitudinal intervention program of first-episode psychosis (PAFIP) conducted at the outpatient clinic and the inpatient unit at the University Hospital Marques de Valdecilla, Santander, Spain. It conformed to international standards for research ethics and was approved by the local institutional review board. The referrals to the PAFIP came from the inpatient unit and emergency room at the University Hospital Marques de Valdecilla, community mental health services, and other community health care workers in Cantabria, Spain. There were no biases in the way patients were referred, and the age-corrected (15–50 years) incidence rate for schizophrenia spectrum disorder was 1.38 per 10,000. A more detailed description of our program has been previously reported.[11]

Subjects

From February 2001 to February 2005, all referrals to PAFIP were screened for patients who met the following criteria: (1) aged 15 to 60 years; (2) living in the catchment area; (3) experiencing their first episode of psychosis; (4) no prior treatment with antipsychotic medication or, if previously treated, a total lifetime of adequate antipsychotic treatment of less than 6 weeks; and (5) meeting DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder. Patients were excluded for any of the following reasons: (1) meeting DSM-IV criteria for drug dependence, (2) meeting DSM-IV criteria for mental retardation, and (3) having a history of neurologic disease or head injury. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID-I) carried out by an experienced psychiatrist 6 months after the baseline visit.[12]

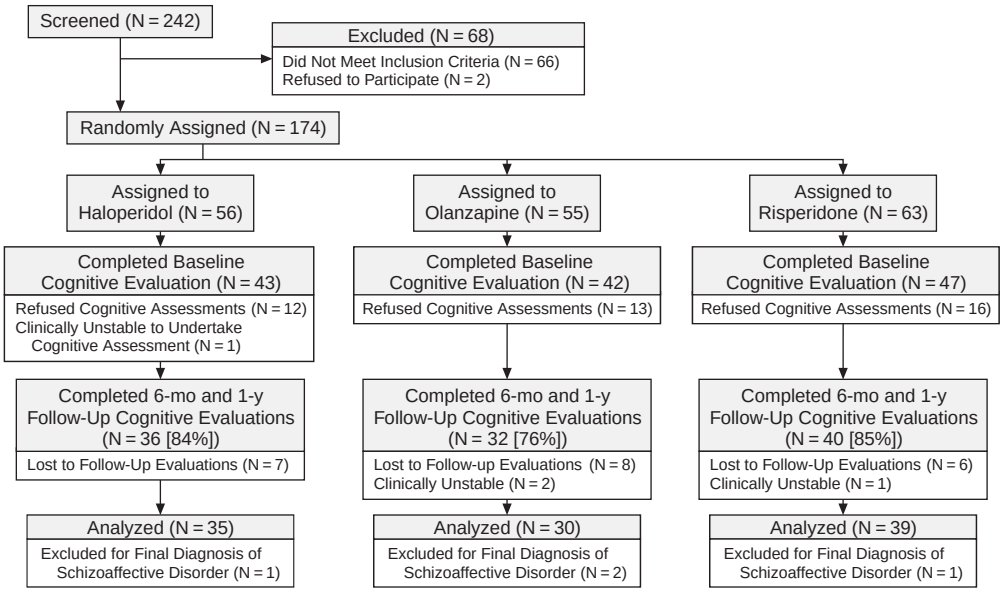
Study Design

This is a prospective, randomized, open-label study that was conducted from February 2001 to February 2005. Patients who agreed to participate underwent a complete evaluation of sociodemographic and clinical variables before being randomly assigned to treatment. We used a simple randomization procedure. A computer-generated randomization list was drawn up by a statistician. At study intake, all but 1 patient were antipsychotic naive. The only patient who was taking antipsychotics at intake underwent a washout period of 5 days before initiating treatment protocol. Dose ranges were 5 to 20 mg/day for olanzapine, 3 to 6 mg/day for risperidone, and 3 to 9 mg/day for haloperidol. At the treating physician's discretion, the dose and type of antipsychotic medication could be changed based on clinical effectiveness and the profile of side effects. Lormetazepam and clonazepam were permitted for clinical reasons. Whenever clinically significant extrapyramidal signs occurred, anticholinergic medication (biperiden at a dose of up to 8 mg/day) was allowed. No anticholinergics were administered prophylactically. Antidepressants (sertraline) and mood stabilizers (lithium) were permitted if clinically needed.

Of the first 174 consecutive patients who met inclusion criteria, 24.1% (N = 42) refused to participate in the cognitive study (Figure 1). Thus, a sample of 132 patients fulfilled baseline cognitive assessment. No significant differences were found in relevant variables, such as age, gender distribution, illness duration, or clinical severity, between those subjects who underwent cognitive evaluations and those who did not wish to take part (all p values > .05).

Of those 132 patients, 24 individuals who did not complete the 1-year follow-up evaluation and 4 schizoaffective patients were excluded from the final analyses. A final set of 104 patients (35 haloperidol, 30 olanzapine, and

Figure 1. Flow Diagram of Participants in the Randomized Clinical Trial



39 risperidone) who underwent baseline and the 2 follow-up cognitive evaluations (at 6 months and at 1 year) were analyzed in this study. No significant sociodemographic and clinical differences were found between patients included in the final analysis (N = 104) and patients who were not included in the final analysis (N = 28) (all p values > .05) (data not shown). Although most of the patients remained on their initial antipsychotic treatment during the study, 9 haloperidol and 3 risperidone patients changed their initially assigned medication at 6 months, and 15 haloperidol, 3 olanzapine, and 7 risperidone patients switched to a different antipsychotic (all atypicals) at 1 year.

At 1-year assessment, patients were receiving haloperidol (N = 20), olanzapine (N = 37), risperidone (N = 33), quetiapine (N = 9), ziprasidone (N = 2), amilsulpride (N = 1), clozapine (N = 1), and perphenazine (N = 1).

Demographic and clinical characteristics of patients and controls are shown in Table 1. Not all patients completed all cognitive tests adequately at baseline and follow-up assessments (see Table 3), owing to their 120-minute duration; therefore, the number of subjects included in each specific cognitive variable varies. Demographic and clinical data of the subset of patients included in each cognitive test are not shown, but are available on request.

In addition, a group of healthy subjects (N = 37) underwent the same cognitive battery as patients. The healthy controls were also tested at 3 points, and the results for cognitive performance of the healthy control groups at baseline and at 6-month and 1-year follow-ups are described in Table 3. The control sample size varies from one test to another due to some cognitive tests' being sporadic, unfinished, or missing (see Table 3). Demographic data from each subgroup of controls included in a given cognitive domain are available on request. Healthy volunteers had no current or past history of psychiatric illness, including substance dependence, neurologic disorders, or general medical disorders, as determined by using an abbreviated version of the Comprehensive Assessment of Symptoms and History.[13] The absence of psychosis in first-degree relatives was assessed by clinical records and family interview. Healthy subjects were not taking anticholinergics or other medications affecting cognitive functioning. After a detailed description of the study, each healthy subject gave written informed consent to participate in accordance with the local ethics committee.

Clinical Assessment

Clinical symptoms of psychosis were assessed by means of the Scale for the Assessment of Positive Symptoms (SAPS)[14] and Scale for the Assessment of Negative Symptoms (SANS).[15] The Calgary Depression Scale (CDS)[16] was used to evaluate depressive symptoms. Extrapyramidal signs were assessed by examinations of patients and scored on the Simpson-Angus Scale[17] and the Barnes Akathisia Scale (BAS).[18] The same trained psychiatrist (B.C.-F.) completed all clinical assessments.

Neuropsychological Assessment

A detailed description of cognitive battery has been described elsewhere (González-Blanch[19] and available from B.C.-F. upon request). Testing was divided into 2 sessions, took approximately 120 minutes, and was given

Table 1. Sociodemographic and Clinical Characteristics in Treatment Groups and Healthy Controls

Characteristic	Haloperidol (N = 35) Mean (SD)	Olanzapine (N = 30) Mean (SD)	Risperidone (N = 39) Mean (SD)	Controls (N = 37) Mean (SD)
Age, y	26.93 (6.70)	27.01 (7.32)	27.42 (8.56)	25.24 (7.87)
Education level, y[a]	10.17 (2.73)	11.2 (3.49)	10.51 (2.96)	11.81 (2.29)
Premorbid IQ[b]	8.71 (2.42)	9.97 (3.32)	9.28 (3.04)	10.28 (2.24)
Duration of untreated illness, mo[c]	22.94 (24.91)	16.71 (25.14)	30.23 (38.08)	NA
Duration of untreated psychosis, mo[d]	8.46 (12.43)	7.39 (12.71)	15.16 (24.72)	NA
SAPS score				
Baseline	13.51 (3.61)	11.97 (4.29)	13.10 (4.45)	NA
1 y	1.11 (1.59)	1.27 (2.78)	1.77 (3.15)	NA
Change	–12.40 (4.04)	–10.70 (5.36)	–11.33 (5.01)	NA
SANS score				
Baseline	6.97 (6.16)	7.60 (7.03)	7.95 (6.35)	NA
1 y	5.66 (5.27)	4.10 (4.37)	5.54 (5.65)	NA
Change	–1.31 (7.40)	–3.50 (8.22)	–2.41 (7.94)	NA
CDS score				
Baseline	2.41 (2.90)	1.67 (2.25)	1.38 (2.42)	NA
1 y	0.65 (1.87)	0.97 (2.43)	0.79 (2.07)	NA
Change	–1.82 (3.08)	–0.70 (3.55)	–0.59 (2.88)	NA
Antipsychotic dose, mg[e]				
6 wk	4.80 (1.67)	15.47 (3.30)	4.18 (1.17)	NA
3 mo	4.13 (1.83)	14.46 (4.53)	4.21 (1.82)	NA
6 mo	3.32 (1.50)	13.04 (4.16)	4.11 (1.84)	NA
1 y	2.75 (1.22)	10.00 (3.66)	3.93 (1.88)	NA
	N (%)	N (%)	N (%)	N (%)
Male	24 (69)	19 (63)	22 (57)	18 (49)
Diagnosis				
Schizophrenia	24 (68)	18 (59)	26 (67)	NA
Schizophreniform disorder	9 (26)	9 (30)	6 (16)	NA
Brief psychotic disorder	1 (3)	2 (7)	5 (12)	NA
Psychosis NOS	1 (3)	1 (3)	2 (5)	NA
Akathisia at 1 y[f]	7 (20)	1 (3)	2 (3)	NA
EPS at 1 y	6 (17)	3 (10)	8 (3)	NA

[a]Patients versus controls: t = –2.21, p = .01.
[b]Premorbid IQ (intelligence quotient) scores estimated from the Wechsler Adult Intelligence Scale-III Vocabulary subtest. Patients versus controls: t = –2.05, p = .04.
[c]Time from the first unspecific symptoms related to psychosis (for such a symptom to be considered, there should be no return to the previous stable level of functioning) to initiation of adequate antipsychotic drug treatment.
[d]Time from the first continuous (present most of the time) psychotic symptom to initiation of adequate antipsychotic drug treatment.
[e]Dose means obtained from those patients who maintained the initial antipsychotic medication throughout the study.
[f]$\chi^2 = 6.61$, p = .037.
Abbreviations: CDS = Calgary Depression Scale, EPS = extrapyramidal side effects, NA = not applicable, NOS = not otherwise specified, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.

in a consistent order. Cognitive testers were blind to medications, adverse event status, and use of concomitant medications. Briefly, the cognitive tests comprised 9 cognitive domains, with outcome measures in parentheses: (1) verbal memory: Rey Auditory Verbal Learning Test (RAVLT) (2 measures were obtained: total number of words recalled over learning trials [learning] and number of words recalled from the list after delay period [long-term recall]); (2) visual memory: Rey Complex Figure Test (RCFT) (long-term recall measure); (3) motor speed: Finger Tapping Test (mean taps in 10 seconds with dominant hand); (4) motor coordination: Grooved Pegboard Test (time to complete with dominant hand); (5) executive functions: Trail Making Test B (TMT-B) (time to complete) and FAS verbal fluency test (number of words in time limit); (6) working memory: Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Backward Digits (total score); (7) speed of processing: WAIS-III Digit Symbol (standard total score); (8) attention: Continuous Performance Test Degraded-Stimulus (total number of correct responses) and Brief Test of Attention (total correct responses); and (9) decision-making capacity: Iowa Gambling Task (difference between advantaged and disadvantaged choices). The WAIS-III vocabulary subtest (number of words generated) was used as a covariate to control the effect of premorbid IQ.

Patients and controls received 3 cognitive assessments throughout the first year: baseline, 6 months, and 1 year. Cognitive baseline assessment was carried out when the clinical status of patients so permitted in order to maximize collaboration, and this occurred at a mean (SD) of 10.5 (3.9) weeks after intake visit. Stabilization of psychotic symptoms and readiness for cognitive evaluation were decided by the clinical team after they interviewed the patient and evaluated the severity of symptoms. Therefore, at baseline cognitive evaluation, the patients

Table 2. Use of Concomitant Medications During Treatment With Haloperidol, Olanzapine, and Risperidone

Concomitant Medication	Haloperidol, N				Olanzapine, N				Risperidone, N			
	Baseline	3 mo	6 mo	1 y	Baseline	3 mo	6 mo	1 y	Baseline	3 mo	6 mo	1 y
Anticholinergics[a]	7	28	21	12	0	1	1	0	2	15	16	12
Benzodiazepines[b]	14	9	9	5	7	6	2	2	14	8	5	7
Hypnotics	1	6	4	2	1	1	1	0	3	3	1	3
Antidepressants	0	1	4	3	0	0	1	1	0	0	2	6
Mood stabilizers	0	0	0	0	0	1	1	1	0	1	1	1

[a]The percentage of patients taking anticholinergics differed among treatment groups at all time points (at baseline, $p = .01$; at 3 mo, 6 mo, and 1 y, $p < .002$).
[b]The percentage of patients taking benzodiazepines at 6 months differed significantly among treatment groups ($p = .047$).

had been on antipsychotic medication for a mean time of 10.5 weeks. Follow-up evaluations were performed at 6 months and at 1 year after initialization of antipsychotic treatment.

Statistical Analyses

Independent sample t tests were used to compare patients and controls on age, years of education, and premorbid IQ. Chi-square (χ^2) tests were utilized to compare frequencies of baseline characteristics. The proportion of patients who were compliant; the frequency of patients who used hypnotics, mood stabilizers, anticholinergics, benzodiazepines, or antidepressants; and the BAS and Simpson-Angus Scale scores were categorically analyzed among groups by χ^2 test.

Observed cases analysis was conducted. Effectiveness analyses were based on intent-to-treat populations, defined as patients who were randomly assigned to a treatment and underwent the 3 follow-up cognitive assessments (baseline, 6 months, and 1 year). In addition, we also conducted an analysis based on per protocol populations, defined as patients who maintained their initial antipsychotic treatment throughout the study. Effect size was calculated as a standardized Z score by dividing the difference between assessment means by the pooled SD.

The primary aim of this study was to test the hypothesis that the 3 antipsychotic treatments would result in different effectiveness to improve cognitive deficits. Repeated-measures analysis of covariance (ANCOVA) was performed for each cognitive variable. For the primary analysis, the between-subject factor was the group (haloperidol, risperidone, and olanzapine) and the within-subject factor was time (baseline, 6 months, and 1 year). Effects of time (longitudinal dimension), group (cross-sectional dimension), and group-by-time (interaction effect) were examined. All post hoc comparisons were Bonferroni corrected. The Greenhouse-Geisser corrections were used when the assumption of sphericity was violated. Secondly, we compared performance of treatment groups with that of the control group. Using the repeated-measures ANCOVA, factors in this model were group (haloperidol, risperidone, olanzapine, and controls) as the between-subject factor and time (baseline and 1 year) as the within-subject factor. A main effect for time in absence of a significant group-by-time interaction would be interpreted as representing practice effects.

In a third set of analyses, we attempted to control the effect of cognitive baseline scores and other relevant sociodemographic variables on cognitive score changes. Treatment groups were compared by means of univariate ANCOVA in change scores. These change scores were calculated for each cognitive domain by subtracting baseline scores from 1-year scores. In this analysis, baseline performance was used as the covariate.

Other secondary variables might have affected cognitive changes. Pearson's exploratory correlational analysis was used to determine the potential associations between the cognitive and clinical change scores (total scores on the SAPS, SANS, and CDS) and the severity of adverse effects (BAS and Simpson-Angus Scale) at 1 year. Owing to the large amount of correlations conducted, the level of significance was set at $p < .01$ for the analysis of correlates.

The Statistical Package for Social Science (SPSS), version 12.0 (SPSS, Inc., Chicago, Ill.), was used for statistical analyses. All statistical tests were 2 tailed, and significance was determined at the .05 level except in the analysis of correlations. No adjustments were made for multiple comparisons.

RESULTS

Demographic and Clinical Characteristics

Relevant sociodemographic and clinical characteristics in treatment groups and healthy subjects are shown in Table 1. The 3 groups had a similar severity of psychopathology at baseline and no differences in the amount of clinical improvement at 1 year. There was a significant difference between treatment groups in the prevalence of akathisia at 1 year ($\chi^2 = 6.61$, df = 2, $p = .037$).

Pharmacologic Treatments

The mean doses at 1 year were 10.0 mg/day (olanzapine), 3.9 mg/day (risperidone), and 2.7 mg/day (haloperidol) (Table 1). The proportion of patients using concomitant medications is summarized in Table 2. At 1-year

Table 3. Performance of the 3 Treatment Groups and Controls on Cognitive Tasks[a]

Test	Outcome Measure	Haloperidol	Olanzapine	Risperidone	Controls
Continuous Performance Test Degraded-Stimulus	Total no. of correct responses				
N		25	17	28	25
Baseline		72.16 (11.08)	73.65 (8.02)	70.61 (11.42)	78.20 (1.61)
6 mo		72.92 (11.21)	75.53 (7.12)	72.64 (11.86)	77.92 (1.73)
1 y		72.16 (13.58)	74.94 (10.53)	74.61 (10.18)	78.84 (1.77)
Brief Test of Attention	Total correct responses				
N		27	22	32	21
Baseline		14.89 (3.61)	15.68 (3.01)	14.87 (3.52)	18.05 (1.83)
6 mo		15.89 (2.76)	15.95 (2.90)	15.53 (2.82)	18.71 (1.11)
1 y		15.74 (3.02)	16.50 (2.98)	16.25 (2.60)	18.52 (1.47)
Grooved Pegboard Test	Time to complete with dominant hand				
N		28	20	33	36
Baseline		72.25 (13.49)	66.25 (11.37)	79.91 (49.33)	57.97 (8.20)
6 mo		68.00 (11.93)	62.45 (8.98)	74.30 (41.06)	53.94 (7.91)
1 y		63.82 (12.04)	59.45 (7.14)	71.94 (44.41)	55.15 (7.42)
Finger Tapping Test	Mean taps in 10 sec with dominant hand				
N		28	19	32	21
Baseline		43.96 (11.47)	49.42 (8.47)	46.80 (11.31)	53.26 (8.24)
6 mo		48.60 (12.11)	49.71 (9.37)	48.72 (8.61)	53.51 (8.59)
1 y		50.07 (9.91)	49.80 (8.40)	46.79 (8.84)	53.83 (7.42)
Rey Auditory Verbal Learning Test (learning)	Total no. of words recalled over learning trials				
N		34	27	37	37
Baseline		37.88 (11.30)	43.52 (12.84)	42.32 (9.50)	52.46 (8.30)
6 mo		43.44 (10.82)	48.93 (12.83)	47.27 (10.14)	56.42 (8.04)
1 y		45.50 (10.82)	48.59 (12.01)	46.76 (10.80)	58.97 (8.26)
Rey Auditory Verbal Learning Test (long-term recall)	No. of words recalled from the list after delay period				
N		34	26	37	37
Baseline		6.44 (3.38)	7.50 (3.94)	7.65 (3.27)	10.84 (2.67)
6 mo		7.94 (3.63)	9.31 (3.56)	8.62 (3.20)	12.05 (2.35)
1 y		8.29 (3.75)	9.69 (3.18)	9.27 (3.88)	12.24 (2.64)
WAIS-III Backward Digits	Total score				
N		34	26	36	36
Baseline		5.29 (1.40)	5.38 (1.79)	6.00 (1.97)	7.47 (2.13)
6 mo		5.79 (1.51)	5.85 (1.46)	6.08 (1.90)	7.55 (1.96)
1 y		6.29 (2.34)	5.88 (1.61)	6.36 (1.85)	7.67 (2.35)
Rey Complex Figure Test	Long-term recall measure				
N		34	26	36	37
Baseline		17.92 (6.47)	18.90 (7.61)	19.20 (6.98)	24.16 (6.42)
6 mo		21.86 (6.27)	22.52 (7.63)	23.19 (6.55)	26.74 (5.68)
1 y		23.42 (7.02)	23.32 (7.47)	23.88 (6.80)	26.31 (6.31)
Trail Making Test B	Time to complete				
N		34	27	37	37
Baseline		105.97 (53.15)	90.11 (45.58)	88.16 (40.43)	58.03 (16.87)
6 mo		95.09 (63.52)	70.11 (39.08)	74.16 (30.10)	51.75 (16.35)
1 y		76.56 (41.70)	72.19 (50.27)	73.08 (32.72)	49.62 (11.48)
WAIS-III Digit Symbol	Standard total score				
N		34	26	35	37
Baseline		6.29 (3.04)	7.38 (2.56)	7.31 (2.96)	10.59 (2.99)
6 mo		7.32 (3.25)	8.96 (2.76)	8.26 (2.90)	12.45 (2.04)
1 y		8.47 (3.53)	9.38 (2.95)	8.77 (2.52)	12.73 (2.02)
FAS verbal fluency test	No. of words in time limit				
N		34	26	35	37
Baseline		30.06 (8.27)	31.65 (12.30)	29.81 (9.95)	38.76 (10.63)
6 mo		30.79 (10.33)	35.42 (11.39)	31.14 (11.86)	43.65 (10.88)
1 y		32.06 (10.89)	37.92 (10.24)	32.49 (10.68)	42.92 (10.85)
Iowa Gambling Task	Difference between advantaged and disadvantaged choices				
N		33	23	33	37
Baseline		–2.97 (26.30)	–0.52 (17.62)	2.97 (27.41)	0.47 (26.04)
6 mo		–4.78 (25.77)	9.13 (36.74)	9.91 (40.98)	19.89 (30.26)
1 y		–0.72 (39.37)	15.30 (42.73)	11.27 (40.37)	32.11 (36.75)

[a]Values are mean (SD) unless otherwise specified.
Abbreviation: WAIS-III = Wechsler Adult Intelligence Scale-Third Edition.

Table 4. Repeated-Measures Analysis of Covariance Comparing Haloperidol, Risperidone, and Olanzapine (intention-to-treat analysis)[a]

		Between-Group Differences		Within-Group Differences		Group-by-Time	
Test	Outcome Measure	F	p	F	p	F	p
Continuous Performance Test Degraded-Stimulus	Total no. of correct responses	0.03	.97	2.81	.07	1.87	.12
Brief Test of Attention	Total correct responses	0.09	.92	2.99	.06	0.48	.75
Grooved Pegboard Test	Time to complete with dominant hand	1.38	.26	22.74	< .001	0.84	.36
Finger Tapping Test	Mean taps in 10 sec with dominant hand	0.58	.56	3.66	.03	3.74	.03
Rey Auditory Verbal Learning Test (learning)	Total no. of words recalled over learning trials	0.63	.53	23.42	< .001	0.70	.59
Rey Auditory Verbal Learning Test (long-term recall)	No. of words recalled from the list after delay period	0.56	.57	30.08	< .001	0.49	.75
WAIS-III Backward Digits	Total score	1.06	.35	5.66	.005	0.76	.55
Rey Complex Figure Test	Long-term recall measure	0.86	.43	37.28	< .001	0.42	.80
Trail Making Test B	Time to complete	0.35	.71	26.45	< .001	1.56	.19
WAIS-III Digit Symbol	Standard total score	0.53	.59	48.40	< .001	1.48	.21
FAS verbal fluency test	No. of words in time limit	0.61	.56	9.40	< .001	0.72	.58
Iowa Gambling Task	Difference between advantaged and disadvantaged choices	1.46	.24	2.57	.08	1.00	.41

[a]Proportion of anticholinergics use and the presence of akathisia at 1 year were used as covariates in all analyses.
Abbreviation: WAIS-III = Wechsler Adult Intelligence Scale-Third Edition.

evaluation, the proportion of patients who required anticholinergics was greater among those receiving haloperidol (N = 12/35, 34.3%) and risperidone (N = 12/39, 30.8%) than those receiving olanzapine (N = 0) (χ^2 = 12.78, df = 2, p = .002). A similar pattern of differences was found at 3- and 6-month evaluations. The cumulative rate of use of antidepressants, mood stabilizers, hypnotics, and benzodiazepines did not differ significantly from one medication to another at any time (Table 2).

The dropout rate at 1 year was positively low in the 3 treatment groups: haloperidol, N = 7 (16.3%); risperidone, N = 7 (14.8%); and olanzapine, N = 10 (23.8%) (χ^2 = 1.32, df = 2, p = 0.512). The overall retention rate was 81.8 % (see Figure 1).

Comparison of Cognitive Change Between Treatment Groups

The results of cognitive performances are described in Table 3. The analysis of between-group differences in the ANCOVA (Table 4) revealed no statistically significant differences in any of the cognitive scores for the 3 treatments at each of the 3 cognitive assessments (all p values > .24). The within-group differences analysis revealed significant time effects (p < .05) in all cognitive domains except Continuous Performance Test Degraded-Stimulus, Brief Test of Attention, and Iowa Gambling Task. The mean performance for all 3 treatment groups significantly improved at 1-year follow-up, with effect sizes ranging from –0.81 to 0.66 in the haloperidol group, from –0.72 to 0.71 in the olanzapine group, and from –0.68 to 0.41 in the risperidone group (see Table 8).

Group-by-time interaction reached significance only on the Finger Tapping Test (F = 3.74, df = 2, p = .03). No other significant group-by-time interaction was found (all p values ≥ .12), as shown in Table 4. The subsequent post hoc analyses suggested that only haloperidol-treated patients displayed a significant score increase on the Finger Tapping Test (F = 9.15, p < .001). Risperidone-treated and olanzapine-treated patients did not improve their Finger Tapping Test scores significantly from baseline to 1-year assessments (p = .16 and p = .96, respectively).

Consistently, the results of univariate ANCOVA showed that there was a significant difference between treatment groups in change score on the Finger Tapping Test (F = 5.24, df = 2, p = .007). No other significant differences were found (all p values ≥ 0.17) (Table 5).

Due to the fact that some of the patients had switched antipsychotic medications during the course of the study, we have also conducted a per protocol analysis of cognitive effectiveness. The results of the repeated-measures ANCOVA and univariate ANCOVA of those patients who maintained their initial antipsychotic medications (per protocol analysis) are described in Table 6. These results were essentially similar to those found in the intent-to-treat analysis, although the analysis of group-by-time interaction on the Finger Tapping Test did not demonstrate significant differences between groups.

Patterns of Cognitive Changes in Controls and Treatment Groups

In a set of secondary analyses, we sought to determine whether the above-mentioned cognitive changes over time in patients were equivalent to practice effects in healthy volunteers. The healthy controls were also tested at 3 time points and the results for cognitive performance of the healthy control groups at baseline, 6 months, and 1-year follow-up are described in Table 3.

Table 5. Results of Analysis of Covariance of Cognitive Score Changes Between Baseline and 1-Year Assessments (intention-to-treat analysis)

		Without Controls[a]		With Controls[b]	
Test	Outcome Measure	F	p	F	p
Continuous Performance Test Degraded-Stimulus	Total no. of correct responses	1.73	.18	1.02	.39
Brief Test of Attention	Total correct responses	0.17	.84	0.83	.48
Grooved Pegboard Test	Time to complete with dominant hand	0.91	.41	0.78	.50
Finger Tapping Test	Mean taps in 10 sec with dominant hand	5.24	.007	3.95	.01
Rey Auditory Verbal Learning Test (learning)	Total no. of words recalled over learning trials	0.04	.67	3.59	.02
Rey Auditory Verbal Learning Test (long-term recall)	No. of words recalled from the list after delay period	0.18	.84	1.03	.38
WAIS-III Backward Digits	Total score	0.88	.42	0.78	.51
Rey Complex Figure Test	Long-term recall measure	1.18	.32	1.48	.22
Trail Making Test B	Time to complete	1.62	.20	3.11	.03
WAIS-III Digit Symbol	Standard total score	1.84	.17	2.24	.09
FAS verbal fluency test	No. of words in time limit	1.39	.25	2.37	.07
Iowa Gambling Task	Difference between advantaged and disadvantaged choices	1.18	.31	1.80	.15

[a]Cognitive baseline scores, akathisia prevalence, and percentage of anticholinergics at 1 year were used as covariates.
[b]Cognitive baseline scores, years of education, and premorbid IQ were used as covariates. Only cognitive baseline scores and years of education were used as covariates for Continuous Performance Test Degraded-Stimulus.
Abbreviation: WAIS-III = Wechsler Adult Intelligence Scale-Third Edition.

The analysis of between-group effects (haloperidol, risperidone, olanzapine, or controls) revealed that the control group had a better cognitive performance than patients (all p values < .05) and that the 4 groups improved cognitive scores over time (1 year) (all p values < .03). The analysis of the group-by-time interaction demonstrated overall significant differences between groups in the patterns of cognitive score change on the Finger Tapping Test ($F = 4.70$, $df = 3$, $p = .004$), TMT-B ($F = 3.11$, $df = 3$, $p = .03$), and RCFT ($F = 3.80$, $df = 3$, $p = .01$) (Table 7). The subsequent post hoc analysis revealed that the improvement in Finger Tapping Test score was significant in the haloperidol-treated patients ($F = 8.99$, $p < .001$). No significant differences were found in the other 2 treatment groups and healthy controls (all p values > .11). With regard to TMT-B and RCFT, the post hoc analysis showed that the 3 treatment groups increased the cognitive scores in both cognitive domains significantly (all p values < .001), whereas healthy controls did not significantly increase their performance in any test ($p > .05$). However, the effect size of differences between baseline and 1 year on TMT-B (haloperidol = 0.61, risperidone = 0.41, olanzapine = 0.37, controls = 0.58) and RCFT (haloperidol = –0.81, risperidone = –0.68, olanzapine = –0.58, controls = –0.33) did not differ significantly between groups (Table 8). For the remaining cognitive tests, the patterns of cognitive score changes across time did not differ among groups, and, therefore, the increase in cognitive scores in the treatment groups could be interpreted as improvements attributed to the effects of practice.

The results of univariate ANCOVA (controlling for baseline scores) showed that there were overall differences between groups in the magnitude of changes in Finger Tapping Test score ($F = 3.95$, $df = 3$, $p = .01$) and RAVLT learning score ($F = 3.59$, $df = 3$, $p = .02$) (Table 5).

Relationship Between Cognitive Change and Clinical Efficacy

We next explored the association of treatment-related changes in cognitive variables and clinical symptom improvements (from baseline to 1 year) through Pearson's correlational analyses. In the olanzapine group, the increase in long-term recall score on the RAVLT was associated with a reduction in SAPS score ($r = –0.530$, $p = .003$). No significant correlations (using a conservative $\alpha = .01$) between clinical and cognitive changes were found in the haloperidol and risperidone groups. The magnitude of these correlations was quite small and ranged, in the olanzapine group, from –0.53 to 0.04; in the risperidone group, from –0.31 to –0.001; and, in the haloperidol group, from –0.02 to 0.39. Overall, the pattern of correlations seems to be similar in the 3 groups of medications.

Relationship Between Cognitive Changes and Adverse Events

The proportion of patients with treatment-emergent extrapyramidal side effects (EPS) at 1 year (a total score higher than 2 on the Simpson-Angus Scale at 1 year, given a total score of 2 or less at baseline) was similar in the 3 treatment groups ($\chi^2 = 2.12$, $df = 2$, $p = .35$). A stratification based on EPS prevalence at 1 year revealed a significant difference on Finger Tapping Test change scores between patients with ($N = 17$) or without EPS ($N = 87$) ($t = –2.20$, $p = .03$). Those individuals with EPS showed a lower improvement on the Finger Tapping Test.

Table 6. Analysis of the Repeated-Measures ANCOVA Comparing Haloperidol, Risperidone, and Olanzapine[a] and the Results of ANCOVA of Cognitive Score Changes Between Baseline and 1-year Assessments (per protocol analysis)

Test	Outcome Measure	Haloperidol, N	Risperidone, N	Olanzapine, N	Repeated-Measures ANCOVA						ANCOVA, Difference Scores	
					Between-Group Differences		Within-Group Differences		Group-by-Time			
					F	p	F	p	F	p	F	p
Continuous Performance Test Degraded-Stimulus	Total no. of correct responses	16	16	21	0.571	.569	2.750	.074	0.364	.784	0.193	.825
Brief Test of Attention	Total correct responses	14	20	26	0.034	.966	4.981	.010	1.676	.161	0.591	.557
Grooved Pegboard Test	Time to complete with dominant hand	15	18	26	1.470	.239	17.479	< .001	0.188	.912	0.249	.780
Finger Tapping Test	Mean taps in 10 sec with dominant hand	16	17	25	0.739	.494	2.400	.101	1.619	.182	2.469	.094
Rey Auditory Verbal Learning Test (learning)	Total no. of words recalled over learning trials	18	24	29	1.360	.264	14.056	< .001	0.227	.923	0.259	.773
Rey Auditory Verbal Learning Test (long-term recall)	No. of words recalled from the list after delay period	18	24	29	1.830	.169	17.827	< .001	0.466	.761	0.926	.401
WAIS-III Backward Digits	Total score	18	23	28	2.599	.082	3.554	.034	0.696	.596	0.494	.623
Rey Complex Figure Test	Long-term recall measure	18	24	29	0.641	.530	28.172	< .001	0.636	.638	0.934	.398
Trail Making Test B	Time to complete	18	24	29	0.638	.532	21.497	< .001	0.996	.405	1.683	.193
WAIS-III Digit Symbol	Standard total score	18	23	27	0.290	.749	31.928	< .001	0.809	.522	1.484	.234
FAS verbal fluency test	No. of words in time limit	18	24	29	0.626	.538	0.792	.002	1.585	.182	2.689	.075
Iowa Gambling Task	Difference between advantaged and disadvantaged choices	18	20	26	0.943	.395	1.279	.286	0.945	.432	1.082	.345

[a]Proportion of anticholinergic use and the presence of akathisia at 1 year were used as covariates in all analyses.
Abbreviations: ANCOVA = analysis of covariance, WAIS-III = Wechsler Adult Intelligence Scale-Third Edition.

No other significant differences on cognitive score changes were found (all p values > .05). A further stratification based on EPS emergence within each treatment group revealed that haloperidol-treated individuals with EPS had a lesser improvement on RCFT (t = –2.08, p = .045) and Finger Tapping Test scores (t = –2.58, p = .02) than haloperidol-treated individuals without EPS. No other significant differences on cognitive change scores between patients with or without EPS in each treatment group were observed.

The percentage of patients with treatment-emergent akathisia at 1 year (BAS global score of 2 or more at 1 year, given a global score of less than 2 at baseline visit) varied between treatment groups: haloperidol (N = 7, 20%), olanzapine (N = 1, 3%), and risperidone (N = 2, 5.1%) (p = .037; see Table 1). A stratification based on akathisia prevalence at 1 year revealed a significant difference on FAS verbal fluency test cognitive change scores between patients with (N = 10) or without akathisia (N = 94) (t = –2.61, p = .01). Patients with akathisia showed a lower FAS verbal fluency test score improvement. No other significant differences in cognitive score changes were found (all p values > .08). A further stratification based on akathisia emergence within each treatment group revealed that haloperidol-treated patients with akathisia showed a lower score improvement in the decision-making capacity, unlike haloperidol-treated patients without akathisia (t = 4.16, p = .01). No other significant differences in cognitive change scores between patients with or without akathisia in each treatment group were observed.

We also examined the association of the severity of EPS (mean score, Simpson-Angus Scale) and akathisia (mean global score, BAS) at 1 year with cognitive changes through Pearson's correlational analyses. Overall, the magnitude of the Pearson correlations was small (ranging from 0.01 to 0.19) and no significant associations were found between the severity of EPS and cognitive score changes. The severity of akathisia showed a slight association with cognitive score changes on the WAIS-III-Digit Symbol (r = –0.21, p = .04) and FAS verbal fluency test (r = –0.27, p = .006). No other significant associations between the severity of akathisia and cognitive score changes were found (all p values > .09).

Relationship Between Cognitive Change and Concomitant Medications

The feasible contribution of concomitant medications on cognitive changes in the 3 groups of treatments was also explored. A significantly different proportion of patients in each treatment group

Table 7. Repeated-Measures Analysis of Covariance Comparing Haloperidol, Risperidone, Olanzapine, and Healthy Controls[a]

Test	Outcome Measure	Between-Group Differences F	Between-Group Differences p	Within-Group Differences F	Within-Group Differences p	Group-by-Time F	Group-by-Time p
Continuous Performance Test Degraded-Stimulus	Total no. of correct responses	2.13	.10	4.57	.04	1.43	.24
Brief Test of Attention	Total correct responses	4.95	.003	7.40	.008	1.02	.39
Grooved Pegboard Test	Time to complete with dominant hand	2.42	.07	49.21	< .001	1.83	.15
Finger Tapping Test	Mean taps in 10 sec with dominant hand	0.76	.52	5.36	.02	4.70	.004
Rey Auditory Verbal Learning Test (learning)	Total no. of words recalled over learning trials	13.32	< .001	67.99	< .001	0.96	.42
Rey Auditory Verbal Learning Test (long-term recall)	No. of words recalled from the list after delay period	11.36	< .001	56.80	< .001	0.35	.79
WAIS-III Backward Digits	Total score	7.24	< .001	11.24	.001	1.43	.24
Rey Complex Figure Test	Long-term recall measure	2.86	.04	81.07	< .001	3.80	.01
Trail Making Test B	Time to complete	4.93	.003	60.16	< .001	3.11	.03
WAIS-III Digit Symbol	Standard total score	16.68	< .001	115.58	< .001	1.61	.19
FAS verbal fluency test	No. of words in time limit	5.91	.001	26.91	< .001	1.38	.25
Iowa Gambling Task	Difference between advantaged and disadvantaged choices	0.76	.52	14.10	< .001	1.83	.15

[a]Years of education, premorbid IQ, and gender were used as covariates in all cognitive variables but Continuous Performance Test Degraded-Stimulus (only years of education was used as covariate).
Abbreviation: WAIS-III = Wechsler Adult Intelligence Scale-Third Edition.

received anticholinergic medication at the time of the 1-year assessment ($\chi^2 = 13.96$, $p < .002$). A stratification based on anticholinergic use at 1 year revealed a significant difference in the change scores of verbal memory (RAVLT total learning [$t = –2.45$; $p = .016$] and RAVLT long-term recall [$t = –2.15$; $p = .03$]), visual memory (RCFT [$t = –3.55$; $p < .001$]), and working memory (WAIS-III Backward Digits [$t = –2.36$; $p = .02$]), with a worse performance in patients with concomitant anticholinergics (N = 24) than patients without anticholinergics (N = 80). No other significant differences in cognitive performance at 1 year were found between groups (all p values > .12).

The cumulative rate of use of antidepressants, mood stabilizers, hypnotics, and benzodiazepines did not differ among the 3 antipsychotic groups at 1 year (see Table 2).

A further stratification based on patients taking anticholinergics within each treatment group revealed only that risperidone-treated patients receiving anticholinergics showed a lower score improvement in working memory (WAIS-III Backward Digits), unlike risperidone-treated patients without anticholinergics ($t = –2.11$, $p = .04$). No other significant differences in cognitive change scores between patients with or without anticholinergics in each treatment group were observed.

DISCUSSION

In a representative sample of patients with first-episode schizophrenia, we found that (1) Patients treated with either risperidone, olanzapine, or a low dose of haloperidol showed a significant improvement in cognitive scores (comprising all cognitive domains) after 1 year; (2) the differential effectiveness of medications on cognition enhancement was, in general, insignificant; (3) cognitive score improvements in patients were, overall, similar to those found in healthy volunteers; and (4) changes in clinical symptoms, the use of concomitant medications, or the presence of motor side effects did not significantly mediate cognitive changes. To the best of our knowledge, this is the first controlled clinical trial that compares long-term (1-year follow-up) cognitive effectiveness of SGAs (olanzapine and risperidone) and FGAs (low-dose haloperidol) in which a group of healthy subjects has also been repeatedly assessed to examine the potential effects of practice.

Consistent with earlier long-term investigations of patients with first-episode schizophrenia treated with low doses of haloperidol,[20] our patients treated with haloperidol showed cognitive score improvements similar to those found in patients treated with risperidone or olanzapine. Similarly, Keefe and colleagues[4] did not find significant differences either between olanzapine and haloperidol in neurocognitive effects after 1 year and 2 years of treatment. In contrast, the short-term analysis (12 weeks) from this sample had revealed a significant benefit of olanzapine compared to haloperidol.[3] Harvey and colleagues[5] also reported in a study with patients who took low doses of risperidone and haloperidol that SGAs (risperidone) were significantly more beneficial than haloperidol, with a greater improvement in general cognitive function and verbal fluency and long-delay free recall in the short term (12 weeks). A couple of additional short-term studies have also found a greater improvement with risperidone relative to haloperidol.[6,7] Purdon et al.[8] described a significantly greater benefit in the general cognitive index (6 cognitive domains) with olanzapine relative to haloperidol and risperidone at 4-month follow-up in a multicenter double-blind randomized study.[8] Taken together, the results from the aforementioned

Table 8. Effect Sizes in Patients (3 groups of treatment) and Healthy Controls Within Each Treatment Period

Test	Outcome Measure	Haloperidol			Olanzapine			Risperidone			Controls		
		0–6 m	6 m–1 y	0–1 y	0–6 m	6 m–1 y	0–1 y	0–6 m	6 m–1 y	0–1 y	0–6 m	6 m–1 y	0–1 y
Continuous Performance Test Degraded-Stimulus	Total no. of correct responses	0.29	0.06	0.32	–0.24	0.06	–0.13	–0.17	–0.17	–0.37	0.16	–0.52	–0.38
Brief Test of Attention	Total correct responses	–0.31	0.05	–0.25	–0.09	–0.18	–0.27	–0.17	–0.26	–0.41	–0.43	0.14	–0.28
Grooved Pegboard Test	Time to complete with dominant hand	0.33	0.34	0.66	0.37	0.37	0.71	0.12	0.05	0.17	0.50	–0.15	0.36
Finger Tapping Test	Mean taps in 10 sec with dominant hand	–0.39	–0.13	–0.57	–0.03	–0.01	–0.04	–0.19	0.22	0.00	–0.03	–0.04	–0.07
Rey Auditory Verbal Learning Test (learning)	Total no. of words recalled over learning trials	–0.50	–0.19	–0.68	–0.42	0.02	–0.40	–0.50	–0.05	–0.43	–0.48	–0.31	–0.78
Rey Auditory Verbal Learning Test (long-term recall)	No. of words recalled from the list after delay period	–0.42	–0.09	–0.52	–0.48	–0.11	–0.61	–0.30	–0.18	–0.45	–0.48	–0.07	–0.52
WAIS-III Backward Digits	Total score	–0.34	–0.25	–0.52	–0.28	–0.02	–0.29	–0.04	–0.15	–0.18	–0.04	–0.05	–0.09
Rey Complex Figure Test	Long-term recall measure	–0.62	–0.23	–0.81	–0.47	–0.10	–0.58	–0.59	–0.10	–0.68	–0.42	–0.26	–0.33
Trail Making Test B	Time to complete	0.18	0.34	0.61	0.47	–0.04	0.37	0.39	0.03	0.41	0.38	0.15	0.58
WAIS-III Digit Symbol	Standard total score	–0.32	–0.34	–0.66	–0.59	–0.14	–0.72	–0.32	–0.18	–0.53	–0.72	–0.13	–0.84
FAS verbal fluency test	No. of words in time limit	–0.08	–0.12	–0.20	–0.32	–0.23	–0.55	–0.12	–0.12	–0.26	–0.45	0.06	–0.38
Iowa Gambling Task	Difference between advantaged and disadvantaged choices	0.07	–0.12	–0.06	–0.33	–0.15	–0.48	–0.20	–0.03	–0.24	–0.68	–0.36	–0.99

Abbreviation: WAIS-III = Wechsler Adult Intelligence Scale-Third Edition.

studies seem to indicate that the greater cognitive improvements associated with SGAs in short-term studies are no longer significant when lengthy periods of follow-up are considered.

Short-term clinical trials in which patients undergo cognitive assessments with short intervals are especially vulnerable to the effect of repeated exposure to the tests and/or assessment environment (i.e., practice effect).[21] It has been stated that haloperidol may exert subtle negative effects on cognition that interfere with practice effects.[22] The greater frequency of emergent EPS, the higher use of anticholinergics to treat EPS, and the marked D_2 receptor blockade in the dorsal striatum may interfere with procedural learning and memory.[23–25] Human and animal studies have consistently shown that drugs with anticholinergic characteristics impair learning and memory.[26] We speculate that the relatively high doses of haloperidol at the first break of the illness may bias the results of short-term cognitive studies toward revealing deleterious cognitive effects owing to the higher prevalence of EPS and the consequent greater use of anticholinergic medications.

Woodward and colleagues[10] concluded in a meta-analysis study that haloperidol does not cause a generalized deficit in the ability to learn from prior exposure, but it may contribute to circumscribed reductions in the practice effects observed in processing speed and working memory (verbal fluency) tests. Likely deleterious effects of haloperidol found in short-term studies might be mediated by the greater interference of practice effect when short intervals between assessments are established. In long-term studies in which the weight of multiple testing would be diminished owing to the lengthy intervals between assessments, these detrimental effects of haloperidol would vanish. Consistently, Keefe and colleagues[3,4] demonstrated that olanzapine treatment produced significantly more cognitive benefit than haloperidol at short term (12 weeks), but they found no evidence of differences in cognitive changes at 1 year and at 2 years. In line with this hypothesis, McGurk and colleagues[27] described that the relative benefits of risperidone on spatial working memory performance at short term was related to the higher use of anticholinergics in haloperidol-treated patients. Harvey et al.[5] also described significantly greater EPS and use of adjunctive medication in the haloperidol group compared to the risperidone-treated patients. Similarly, Purdon et al.[8] also described that a significantly greater proportion of patients taking haloperidol (73.3%) required anticholinergic treatment relative to risperidone (45%) and olanzapine (15%). It is of note that a stratification based on anticholinergic use in our sample revealed that those patients receiving anticholinergics at 1 year showed lower cognitive score changes in memory and verbal fluency tests than patients who did not receive anticholinergics. The anticholinergic medications may differentially interfere with cognitive gains in longitudinal

studies depending on the weight of practice effects on cognitive test performance.

Likewise, other feasible reasons should be considered to explain the inconsistencies regarding the cognitive effects of FGAs and SGAs. It may also be argued that relatively high doses of haloperidol might mask practice effect and therefore the previously reported positive effects of SGAs may be due to too high doses of haloperidol in the control arms. Contrary to this assumption, in a recent meta-analysis, Woodward et al.[10] found no evidence that higher doses of haloperidol themselves may be associated with lower cognitive score improvements. The dose of haloperidol used in our study (2.7 mg) is relatively low compared to the range of doses used in previous investigations in first-episode schizophrenia.

A secondary goal of this study was to investigate whether cognitive changes in the 3 groups of patients were similar or different to cognitive changes attributed to repeated exposure to cognitive tests in healthy controls. Most cognitive score changes in our treatment groups are similar to practice effects in healthy controls and therefore might be due to practice effect rather than true improvements in the compromised neurocognitive function. However, 3 cognitive variables demonstrated a rate of improvement above and beyond practice effects: Finger Tapping Test, TMT-B, and RCFT. However, it is worth noting that the effect size of differences between baseline and 1 year on TMT-B and RCFT, ranging from medium to moderate, did not differ between groups (see Table 8). The weight of practice effects has not been examined in other previous studies of first-episode schizophrenia investigating the differential effects of antipsychotic medications on cognition.

Our results here, including a group of haloperidol-treated patients who were followed up for 1 year are consistent with and extend those reported by Goldberg and colleagues,[9] who observed that, in general, the cognitive score improvements found in first-episode patients treated with risperidone or olanzapine were consistent in magnitude with practice effects observed in healthy controls at 16 weeks. Furthermore, they also described that, in 2 cognitive variables, the performance gains in the schizophrenia group exceeded the practice effects in controls: visual episodic memory and the Trail Making Test. If the above is taken together with our results, we might speculate that antipsychotics produce significant and valid cognitive improvements in memory and executive function tests that require the integration of visual perceptual skills and motor speed. We have also explored the likelihood that the presence of a ceiling effect in the cognitive performance of the control group would produce type II error inflation. The analysis of distribution of control subjects revealed that only 48.65% of the subjects were in the upper quartile (> 26) on the RCFT so they still may have left room for improvement (analysis available from B.C.-F. upon request). Consistently, the analysis of effect size of differences in score between baseline and 1-year on the Finger Tapping Test (–0.07), TMT-B (0.58), and RCFT (–0.33) showed that effect sizes in the control group are in a similar range to those in patients (see Table 8).

The beneficial effect of haloperidol on the Finger Tapping Test was an unexpected finding. It may be argued in line with our previous hypothesis that the higher doses of haloperidol, higher EPS prevalence, and increased adjunctive anticholinergics at the very first weeks of treatment might remarkably impair baseline Finger Tapping Test performance (see Table 3). The progressive reduction of haloperidol doses and use of anticholinergics during the follow-up period (see Table 1) would lessen the negative effects of haloperidol on motor speed and therefore result in a greater performance increase. Consistently, our correlational analysis showed that the severity of EPS was associated with poorer Finger Tapping Test and RCFT performance exclusively in haloperidol-treated patients. Additionally, the effect sizes for motor speed in the haloperidol group were larger in the baseline to 6-month period (–0.39) than in the 6-month to 1-year period (–0.13). The greater size effect is coincident with a higher reduction of haloperidol doses (Table 1) and anticholinergic use (Table 2). This differential pattern of changes was not found in the other 2 treatment groups or the control group. It is worth noting that at 1 year there were no significant differences between groups in motor speed scores.

Due to the fact that 15 haloperidol-treated patients switched medication during the follow-up and that, per protocol, analysis did not reveal significant differences between treatments in Finger Tapping Test, we have also explored the likelihood that these results might be biased by the confounding effect of the switch of medications. However, the direct comparison of those haloperidol patients who maintained treatment and those who switched medication did not show group-by-time interaction on the Finger Tapping Test ($F = 0.124$, $df = 2$, $p = .884$) (analysis available from B.C.-F. upon request), suggesting that the beneficial effect of haloperidol in motor speed does not seem to be biased by the switch of medication during the follow-up.

There were a few limitations to this study. First, the fact that our patients had been on antipsychotic medications for a mean of 10.5 weeks before the baseline cognitive evaluation does not permit us to explore possible differences in cognitive effectiveness between treatments in the short term. Most of the previous literature studying the effectiveness of antipsychotics on cognition explored cognitive changes in drug-naive patients during short periods of time (range from 6 to 16 weeks). Second, it has to be borne in mind that the lack of a group of drug-free patients in which practice effects would have been assessed limits our capacity to fully ascertain to what extent cognitive score changes are related to practice effects, medication effects, or illness itself. Hence, our results herein

should be considered as inferential. A final limitation of our study was the open-label design, as this would have led to some data bias and potentially to some bias in the interpretation of the results. Despite these limitations, we believe this study to be a very thorough investigation of the differential cognitive effectiveness of FGAs and SGAs in first-episode nonaffective psychosis individuals who are representative of clinical practice and who are treated in routine clinical settings. The low rate of dropouts (i.e., < 19%) and the long follow-up period add strength to the conclusions drawn from this study.

In conclusion, haloperidol, olanzapine, and risperidone showed an equal effectiveness for improving the cognitive deficits present at early stages of psychosis. In general, the magnitude of cognitive score improvements observed with antipsychotics was compatible with the improvements due to repeated exposure to tests. The study also underscores the importance of examining the impact of EPS and anticholinergic medication in longitudinal efficacy studies. We believe that our results provide important information regarding the practical utility of antipsychotic treatments to improve cognition and thus may contribute to developing novel approaches for cognitive pharmacotherapy in schizophrenia.

Drug names: biperiden (Akineton), clonazepam (Klonopin and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), ziprasidone (Geodon).

REFERENCES

1. Keefe RS, 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
2. Woodward ND, Purdon SE, Meltzer HY, et al. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. Int J Neuropsychopharmacol 2005;8: 457–472
3. Keefe RS, Seidman LJ, Christensen BK, et al. 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
4. Keefe RS, Seidman LJ, Christensen BK, et al. Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. Biol Psychiatry 2006;59:97–105
5. Harvey PD, Rabinowitz J, Eerdekens M, et al. 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
6. Schuepbach D, Keshavan MS, Kmiec JA, et al. Negative symptom resolution and improvements in specific cognitive deficits after acute treatment in first-episode schizophrenia. Schizophr Res 2002;53:249–261
7. Lee SM, Chou YH, Li MH, et al. Effects of antipsychotics on cognitive performance in drug-naive schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:1101–1107
8. Purdon SE, Jones BD, Stip E, et al. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. Arch Gen Psychiatry 2000;57:249–258
9. Goldberg TE, Goldman RS, Burdick KE, et al. Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? Arch Gen Psychiatry 2007;64:1115–1122
10. Woodward ND, Purdon SE, Meltzer HY, et al. A meta-analysis of cognitive change with haloperidol in clinical trials of atypical antipsychotics: dose effects and comparison to practice effects. Schizophr Res 2007;89:211–224
11. Crespo-Facorro B, Perez-Iglesias R, Ramirez-Bonilla M, et al. A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis. J Clin Psychiatry 2006(10);67:1511–1521
12. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Non-Patient Edition. New York, NY: Biometrics Research Department; 2001
13. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH): an instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 1992;49:615–623
14. Andreasen NC. Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, Ia: University of Iowa Press; 1984
15. Andreasen NC. Scale for the Assessment of Negative Symptoms (SANS). Iowa City, Ia: University of Iowa Press; 1984
16. Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. Br J Psychiatry Suppl 1993;22:39–44
17. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
18. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
19. González-Blanch C, Crespo-Facorro B, Alvarez-Jiménez M, et al. Cognitive dimensions in first-episode schizophrenia spectrum disorders. J Psychiatr Res 2007;41:968–977
20. Green MF, Marder SR, Glynn SM, et al. The neurocognitive effects of low-dose haloperidol: a two-year comparison with risperidone. Biol Psychiatry 2002;51(12):972–978
21. McCaffrey RJ, Duff K, Westervelt HJ. Practitioner's Guide to Evaluating Change With Neuropsychological Assessment Instruments. New York, NY: Kluwer Academic/Plenum Publishers; 2000
22. Carpenter WT, Gold JM. Another view of therapy for cognition in schizophrenia. Biol Psychiatry 2002;51(12):969–971
23. Kumari V, Corr PJ, Mulligan OF, et al. Effects of acute administration of d-amphetamine and haloperidol on procedural learning in man. Psychopharmacology (Berl) 1997;129:271–276
24. Ramaekers JG, Louwerens JW, Muntjewerff ND, et al. Psychomotor, cognitive, extrapyramidal, and affective functions of healthy volunteers during treatment with an atypical (amisulpride) and a classic (haloperidol) antipsychotic. J Clin Psychopharmacol 1999;19:209–221
25. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry 2000;157: 514–520
26. Levin ED. Psychopharmacological effects in the radial-arm maze. Neurosci Biobehav Rev 1998;12:169–175
27. McGurk SR, Green MF, Wirshing WC, et al. Antipsychotic and anticholinergic effects on two types of spatial memory in schizophrenia. Schizophr Res 2004;68:225–233