Cognitive Effects of Antipsychotic Drugs in First-Episode Schizophrenia and Schizophreniform Disorder: A Randomized, Open-Label Clinical Trial (EUFEST)

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Objective: Cognitive impairment, manifested as mild to moderate deviations from psychometric norms, is present in many but not all schizophrenia patients. The purpose of the present study was to compare the effect of haloperidol with that of second-generation antipsychotic drugs on the cognitive performance of patients with schizophreniform disorder or first-episode schizophrenia.

Methods: Subjects were 498 patients with schizophreniform disorder or first-episode schizophrenia who were randomly assigned to open-label haloperidol (1 to 4 mg/day [N=103]), amisulpride (200 to 800 mg/day [N=104]), olanzapine (5 to 20 mg/day [N=105]), quetiapine (200 to 750 mg/day [N=104]), or ziprasidone (40 to 160 mg/day [N=82]). The Rey Auditory Verbal Learning Test, Trail Making Test Part A and Part B, WAIS Digit Symbol Test, and Purdue Pegboard Test were administered at baseline and the 6-month follow-up evaluation.

Results: Compared with scores at baseline, composite cognitive test scores improved for all five treatment groups at the 6-month follow-up evaluation. However, there were no overall differences among the treatment groups. In addition, there was a weak correlation between the degree of cognitive improvement and changes in Positive and Negative Syndrome Scale scores.

Conclusion: Treatment with antipsychotic medication is associated with moderate improvement in the cognitive test performance of patients who have schizophreniform disorder or who are in their first episode of schizophrenia. The magnitude of improvement does not differ between treatment with haloperidol and treatment with second-generation antipsychotics. Moreover, cognitive improvement is weakly related to symptom change.

A considerable proportion of patients with schizophrenia perform an average of 1.5 to 2.5 standard deviations below population norms on standardized psychometric tests, a performance consistent with mild to moderate cognitive impairment (1–3). Other patients perform within age-adjusted norms, yet their performance is worse than predicted based on parental education (4). The cognitive impairment often appears before the onset of psychosis (5–7), persists throughout the patient's life regardless of remission of psychosis, and is correlated with functional outcomes (8, 9). For all these reasons, cognitive impairment in schizophrenia is an important target for therapeutic intervention (10, 11). However, despite the importance of cognitive dysfunction to outcome in schizophrenia, the benefit exerted by antipsychotic medications on cognitive performance remains questionable (12, 13).

Investigation of the cognitive effects of antipsychotics intensified after the introduction of second-generation ("atypical") antipsychotic drugs. It has been hypothesized that second-generation antipsychotic drugs differ in their mechanism of action relative to first-generation antipsychotic drugs. The equivocal results of the plethora of individual studies and meta-analyses comparing the effects of second-generation antipsychotic drugs with those of first-generation antipsychotic drugs on cognitive performance reflect the unresolved debate regarding this issue. Some

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studies reported that the cognitive benefits of second-generation antipsychotics were superior to those of first-generation antipsychotics (12, 22–21), but the effect size of these differences was not large and the results were inconsistent. Furthermore, the sample size of some of these trials was small, the statistical analyses employed were not always preplanned, and these trials did not always properly account for relevant confounders such as symptom change, anticholinergic treatment, change in extrapyramidal symptoms, and practice (14, 16, 21–23). Additionally, in many of these trials the investigator(s) or sponsor(s) selected a relatively high dose of the first-generation antipsychotic drug as the comparator, which might have biased the results in favor of the second-generation antipsychotic drug, since high doses of first-generation antipsychotics both impair motor performance and require anticholinergic drugs, which in turn may impair cognitive performance (13). Finally, many of the studies of the cognitive effects of second-generation antipsychotic drugs were funded by companies that manufacture these medications, a fact cited by some investigators as a possible source of bias (24). The doubts about the superior procognitive effects of second-generation antipsychotic drugs, taken together with doubts regarding the advantages of these drugs in other noncognitive areas of schizophrenia, became the impetus for several publicly funded trials intended to provide more definitive answers. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (25), funded by the U.S. government, addressed many of these biases. In a preplanned analysis, the CATIE study reported that although cognitive performance improved in all groups after 2 months of treatment with olanzapine, perphenazine, quetiapine, or risperidone, there were no statistically significant differences among the groups (26). Despite the many strengths of the CATIE trial, the following arguments were raised: 1) chronically ill patients are less likely to benefit from the procognitive advantages of second-generation antipsychotics than younger first-episode schizophrenia patients, since chronically ill patients who participate in trials often do so because they failed to respond to previous treatment(s); 2) haloperidol, which is the most prescribed first-generation antipsychotic, should have been used as the comparator instead of perphenazine, which has many characteristics of second-generation antipsychotics (27) and is much less prescribed; 3) results obtained from blinded trials are not generalizable, since patients who participate in such trials are different from the patients seen in clinical practice; and 4) in blinded trials, the psychiatrist is deprived of the possibility to adjust the optimal dose to the individual patient.

The present study addresses some of the aforementioned limitations of the CATIE study by comparing the cognitive performance of first-episode patients randomly assigned in an open-label design to haloperidol or one of four second-generation antipsychotics (amisulpride, olanzapine, quetiapine, and ziprasidone). Since it has been argued that trials showing second-generation antipsychotics to be superior to haloperidol used doses of haloperidol that were too high, the drug was administered in the low dose of 1 to 4 mg/day. To improve the study's generalizability and acceptability to patients and treating physicians, the design was pragmatic and included patient groups that are often excluded in efficacy trials (e.g., patients with substance misuse and patients who could not participate in blinded trials for safety or other reasons). The overall objective of this randomized, open-label trial was to compare the effectiveness of haloperidol with that of second-generation antipsychotics as reflected by the time to discontinuation of the randomized drug. The study (European First Episode Schizophrenia Trial [EUFEST]) has been described in detail elsewhere (28, 29).

Method

Participants (N=498) were 18- to 40-year-old patients who met DSM-IV criteria for schizophrenia or schizophreniform disorder, confirmed using the Mini-International Neuropsychiatric Interview–Plus (30), and were recruited at 50 sites in 13 European countries and Israel.

Inclusion criteria were 1) recent onset of psychosis with <2 years between the onset of positive symptoms and recruitment into the trial; 2) <2 weeks exposure to antipsychotic drugs during the preceding year, and 3) <6 weeks lifetime exposure to antipsychotic drugs. Data were obtained on demographics, diagnoses, severity of psychopathology (Positive and Negative Syndrome Scale [PANSS] [31], Clinical Global Impression [CGI] Scale [32]), and extrapyramidal symptoms (St. Hans Rating Scale [33]). The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and national regulatory requirements.

Patients were randomly assigned via a centralized, computerized online randomization system to open-label treatment with haloperidol, 1 to 4 mg/day (N=103); amisulpride, 200 to 800 mg/day (N=104); olanzapine, 5 to 20 mg/day (N=105); quetiapine, 200 to 750 mg/day (N=104); or ziprasidone, 40 to 160 mg/day (N=82). (Ziprasidone was not available in all participating countries at all times throughout the trial, which explains the smaller number of patients in this arm.) At all times during the trial, the dose administered to patients was at the discretion of the treating physician, providing that it remained within the range permitted by the protocol. Mood stabilizers, benzodiazepines, antidepressants, and anticholinergics were allowed before and during the trial. Additional antipsychotics were not permitted.

The following five cognitive tests were administered:

Rey Auditory Verbal Learning Test. This assessment is a list learning task in which the participants are read a list of words and are then tested for what they have learned by recall. Five trials are administered, and the outcome measure is the total number of words recalled (34).

Trail Making Test, Part A and Part B (two tests). These assessments are tests in which participants must first draw lines to connect consecutively numbered circles on one worksheet (Part A) and then connect the same number of consecutively numbered and lettered circles on another worksheet by alternating between the two sequences (Part B). The outcome measures are the time to complete the tests. These are tests of complex visual scanning, motor speed, and ability to shift strategy (35).

Purdue Pegboard Test. This assessment is a task in which participants must place pegs in the holes of a board. It tests motor speed and motor coordination and is sensitive to subtle motor dysfunction, including extrapyramidal symptoms. The outcome

TABLE 1. Demographic and Baseline Characteristics of Patients With Schizophreniform Disorder or First-Episode Schizophrenia

| | Group | | | | Analysis | | |
| | Subjects With Complete Data (included in the analyses) (N=286) | | Subjects With Incomplete Data (excluded from the analyses) (N=212) | | | | |
Characteristic	Mean	SD	Mean	SD	t	df	p
Age (years)	25.73	5.3	26.32	5.8	1.18	496	0.24
Education (years)	12.71	2.9	12.12	2.9	–2.24	491	0.03
PANSS score	88.00	20.3	89.27	21.1	0.67	485	0.51
Cognitive z score (baseline)							
Composite score	0.04	0.7	–0.09	0.9	–1.67	456	0.1
Trail Making Test Part A[a]	0.10	0.8	–0.16	1.3	–2.42	454	0.02
Trail Making Test Part B[a]	0.01	1.0	–0.02	1.0	–0.33	432	0.74
WAIS-III Digit Symbol	0.02	0.9	–0.04	1.1	–0.66	445	0.51
Purdue Pegboard Test	–0.01	1.03	0.02	0.9	0.31	440	0.76
Rey Auditory Verbal Learning Test	0.08	0.96	–0.13	1.05	–2.10	430	0.04

[a] Scores were reversed, and thus higher scores are indicative of better performance.

measure is the number of pegs placed correctly within 30 seconds by the dominant hand drawn (36).

Digit Symbol Coding. This assessment is a test in which the participant is allowed 120 seconds to move through a grid of 133 numbers (1 to 9) and pair them with the correct symbol by using a key consisting of nine symbol-digit pairs. The test is part of the WAIS-III (37) and measures symbolic representational abilities, visual motor skill/dexterity, processing speed, attention/concentration, visual perception of abstract stimuli, and short-term visual memory. The outcome measure is the number of correct symbols drawn within 120 seconds (37).

The composite score, rather than the individual test scores, was assigned as the main outcome measure to increase statistical power. The five cognitive tests were selected based on practicality of administration for a large, multisite, international, multilingual, schizophrenia antipsychotic clinical trial. Motor abilities were emphasized in order to assess the effect of haloperidol on cognitive performance. All of the countries that participated had validated versions of the tests, except Bulgaria for the Rey Auditory Verbal Learning Test. Since lengthy testing is not always acceptable to patients, the tests selected represent a compromise between the comprehensiveness of the test battery and the desire to reduce the amount of missing data. The tests were administered at baseline and after 6 months of treatment (SD=3 weeks). For patients in whom the severity of psychosis at baseline was such that cognitive testing was not feasible, testing could be postponed until the end of the first month of the trial. The tests were administered by psychologists and psychiatrists trained at investigators meetings to administer the specified tests.

Of the 498 patients randomly assigned to one of the five trial drugs, 40 were missing baseline data and 172 completed ≤2 of the five neurocognitive tests at both time points and were therefore excluded from analyses using the composite score. The remaining 286 patients included in the analysis had valid data at baseline and again at 6 months for ≥3 of the five neurocognitive assessments. Analyses regarding each subtest included all patients who had valid data for the specific test at both baseline and the 6-month follow-up. Comparison of demographics and clinical characteristics between the group of 286 patients included in the composite score analyses and the group of 212 patients excluded from these analyses as a result of incomplete data revealed that excluded patients were less educated and had worse cognitive performance on two of the individual tests, but these differences were very small (Table 1). Chi square tests revealed no differences in the distribution of gender and race between the group of included patients and the group of excluded patients. Before receiving trial medica-

tion, of the 286 patients included in the analyses, 29% were antipsychotic naive, 24.5% had received treatment with a first-generation antipsychotic drug, and 46.5% had received treatment with a second-generation antipsychotic drug. Comparisons among the patients randomly assigned to the five medication arms revealed no baseline differences on demographic characteristics (Table 2). There were no differences in rates of extrapyramidal symptoms between the five study arms, except patients who were randomly assigned to haloperidol exhibited more akathisia (χ^2=9.77, df=4, p=0.04), but these differences were very small.

Before randomization to the trial medication, 11.2% of patients were already receiving anticholinergic drugs as treatment for extrapyramidal symptoms resulting from medications taken before the present study. During the 6-month period between randomization and follow-up, anticholinergic drugs were added to the treatment regimen of an additional 18.5% of the participating patients. At the time of the 6-month follow-up, the mean daily antipsychotic doses were as follows: 2.5 mg for haloperidol, 455 mg for amisulpride, 12 mg for olanzapine, 458 mg for quetiapine, and 98 mg for ziprasidone.

Statistical Analyses

To analyze the results, a composite score of the five neurocognitive tests was defined as the mean of the patients' results on all tests. Scores were standardized to create z scores (mean=0 [SD= 1]) based on the means and standard deviations on the baseline assessments of the 286 patients included in the analyses. Effect size was calculated using Cohen's formula (38). The Pearson correlation between baseline and the end-of-trial score was 0.79, indicating high within-subject consistency of the composite score. Within-group improvement in cognitive performance over time was evaluated using paired-sample t tests. Secondary analyses compared change in the five standardized test scores between baseline and month 6 and included all patients who had valid data for the specific test at both baseline and the 6-month follow-up. Treatment groups were compared using analysis of covariance and independent-sample t tests with Bonferroni corrections for multiple comparisons. Linear regression analysis was used in an attempt to predict improvement in the cognitive composite score from baseline to 6 months. Cox proportional hazards regression analyses were performed to examine the association between change in the cognitive composite score from baseline to month 6 and time to all-cause discontinuation or time until discontinuation as a result of lack of efficacy. The statistical analysis, similar to the method described by Keefe et al. (26), was determined before access to the cognitive data was available.

TABLE 2. Baseline Characteristics of 286 Patients With Schizophreniform Disorder or First-Episode Schizophrenia by Randomly Assigned Treatment Arm

Characteristic	Haloperidol (N=52)		Amisulpride (N=55)		Olanzapine (N=74)		Quetiapine (N=60)		Ziprasidone (N=45)		Analysis		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p
Age (years)	26.03	5.8	24.67	4.2	26.07	5.6	26.18	5.2	25.56	5.9	0.75	4, 281	0.56
Education (years)	12.71	2.2	12.89	2.8	13.07	3.5	12.28	3.1	12.47	2.3	0.74	4, 280	0.56
PANSS score	91.35	19.4	85.22	18.9	86.80	21.4	90.08	21.7	86.76	19.5	0.87	4, 281	0.48
	N	%	N	%	N	%	N	%	N	%	χ^2	df	p
Gender											5.09	4	0.28
Male	32	61.5	29	52.7	42	56.8	40	66.7	21	46.7			
Female	20	38.5	26	47.3	32	43.2	20	33.3	24	53.3			
Race											3.59	4	0.47
Caucasian	48	92.3	54	98.2	70	94.6	59	98.3	43	95.6			
Other	4	7.7	1	1.8	4	5.4	1	1.7	2	4.4			

Results

Change in the cognitive composite score from baseline to 6 months showed improvement in each of the five treatment groups (haloperidol: t=–3.43, df=51, p=0.001 [effect size=0.43]; olanzapine: t=–7.11, df=73, p<0.001 [effect size=0.56]; quetiapine: t=–6.25, df=59, p<0.001 [effect size=0.51]; ziprasidone: t=–4.75, df=44, p<0.001 [effect size=0.49]; and amisulpride: t=–4.15, df=54, p<0.001 [effect size=0.33]). There was no overall difference between the five treatment groups in the composite scores (F=0.56, df=4, 281, p=0.69) or individual tests (all p values >0.11) (Table 3). Random effects analyses, including subjects with partial missing data, yielded similar results. A significant improvement in the cognitive composite score was seen over time (p<0.001), but there were no differences between the five study arms (p=0.42). Controlling for multiple comparisons using Bonferroni corrections, t tests comparing the change in the subtest scores from baseline to month 6 for haloperidol versus the four second-generation antipsychotic drugs (both separately and grouped together) revealed no significant differences.

Since there were no differences among the five treatment groups on the cognitive composite and subtest scores, presentation of the individual measures at baseline and the 6-month follow-up included all patients who had valid data for both time points collapsed across treatment groups (Table 4). Change in the individual measures showed consistent improvement.

Changes in the effect size of the composite scores of patients who were drug naive before baseline testing did not differ significantly from that of patients who received drug treatment before baseline testing (effect size=0.37 [SD=0.58] versus effect size=0.45 [SD=0.65], p=0.31, respectively).

The analyses were repeated with trial site, years of education, and baseline alcohol and substance use included in the model. These covariates did not produce results that differed significantly from the unadjusted analyses.

A model of prediction of improvement in the cognitive composite score from baseline to 6 months suggested that a lower (worse) baseline composite score was a predictor of greater cognitive improvement (r^2=0.25, p<0.001). Drug and alcohol abuse, trial site, and PANSS subscale scores were not significant predictors of cognitive improvement. Similar results were found when examining each of the five study arms separately.

The Pearson correlations between change in the cognitive composite score from baseline to the 6-month follow-up and change in PANSS scores from baseline to the 6-month follow-up revealed negative correlations (Table 5). These negative correlations indicated that cognitive improvement was associated with symptom amelioration, but the magnitude of these correlations was very small. Changes in the composite scores of the 53 patients for whom anticholinergic medications were added between the baseline and 6-month assessments did not differ from that of the rest of the patients (effect size=0.43 [SD=0.6] versus effect size=0.41 [SD=0.75], respectively).

Cox proportional hazards regression analyses suggested that change from baseline to 6 months in the cognitive composite score was not a significant predictor of time to discontinuation as a result of efficacy (p=0.99) or time to all-cause discontinuation (p=0.96). The results were unchanged when baseline covariates that were found previously to predict time to discontinuation were included (26).

Discussion

The present study compared cognitive performance in first-episode schizophrenia patients after 6 months of treatment with haloperidol, olanzapine, amisulpride, ziprasidone, or quetiapine. Compared with the results of baseline testing, cognitive scores improved moderately, with no differences among the five treatment groups. Lower (worse) baseline composite scores predicted greater cognitive improvement. Change in cognitive performance was weakly related to change in symptom scores.

Results of this randomized, open-label trial, reporting small advantages of second-generation antipsychotic drugs relative to first-generation antipsychotic drugs in terms of cognitive performance, differ from findings of some previous studies and meta-analyses (22–21). A likely explanation for this difference might be the relatively high

TABLE 3. Cognitive Measure Changes From Baseline to 6 Months (z scores) by Treatment Group

Measure	Haloperidol			Olanzapine			Quetiapine			Amisulpride			Ziprasidone			Analysis		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	F	df	p
Composite score[a]	52	0.36	0.76	74	0.46	0.55	60	0.50	0.62	55	0.35	0.63	45	0.44	0.62	0.56	4, 281	0.69
Trail Making Test Part A[b]	59	0.23	0.82	81	0.28	0.73	66	0.27	0.47	66	0.27	0.90	48	0.29	0.62	0.06	4, 315	0.99
Trail Making Test Part B[b]	55	0.13	0.42	81	0.33	0.60	66	0.25	0.44	66	0.45	1.41	48	0.32	0.83	1.29	4, 311	0.28
WAIS-III Digit Symbol	58	0.22	0.80	80	0.39	0.71	64	0.48	0.64	66	0.36	0.71	48	0.41	0.73	1.04	4, 311	0.39
Purdue Pegboard Test	59	0.32	0.90	81	0.25	0.76	63	0.34	0.77	64	0.19	0.78	46	0.02	0.84	1.34	4, 308	0.26
Rey Auditory Verbal Learning Test	56	0.38	0.87	78	0.51	0.68	58	0.38	1.01	62	0.45	0.97	44	0.62	0.82	0.64	4, 293	0.64

[a] The composite scores were calculated only for the 286 subjects who completed at least three out of the five cognitive tests.
[b] Scores were reversed, and thus higher scores are indicative of better performance.

doses of haloperidol used in some, but not all, related studies (13). High doses increase the risk of extrapyramidal symptoms and the use of anticholinergic medications, which in turn impair motor and cognitive speed. It is therefore possible that results of previous trials comparing second-generation antipsychotics with first-generation antipsychotics on cognitive functioning in schizophrenia in fact reflect the diminished propensity of second-generation antipsychotics to induce extrapyramidal symptoms rather than an intrinsic cognitive benefit of these new compounds. In the present trial, the mean daily dose of haloperidol was only 2.5 mg, which is a lower dose than that used in most other studies.

Results of the present trial are in agreement with the results of the CATIE schizophrenia trial, which reported cognitive improvements after 2, 6, and 18 months of treatment, relative to baseline, but no differences among treatment groups, with the exception of a slight advantage for perphenazine (26). The larger effect sizes reported in the present study compared with that of the CATIE study could be attributable to the younger and less chronic population examined in our study. The magnitude of the improvement observed in the present study is similar to that reported in other studies of first-episode schizophrenia patients (15, 39, 40). One single study (39) of first-episode patients reported a very small advantage of risperidone over haloperidol, but the advantage was extremely small and the dose of haloperidol was higher than the dose used in the present trial.

Part of the improvement in cognitive test scores between baseline and 6-month testing observed in the current study might have been a result of practice or placebo effects (41), such as prior exposure to the tests, familiarity, and procedural learning. This was demonstrated in a recent study, conducted by Goldberg et al. (23), in a sample of first-episode schizophrenia patients treated with second-generation antipsychotics as well as in a comparison sample of healthy subjects, reporting the same order of magnitude of improvement found in the present study (i.e., effect size=0.33). In the present trial, the changes between the baseline and 6-month assessments ranged from

an effect size of 0.56 to 0.33, depending on the individual test. Although patients were tested more often in the study conducted by Goldberg et al. (23) than in the present study, it is still possible that at least part of the improvement observed in the current trial might have been the result of practice. Thus, the 6 months that elapsed between testing was sufficiently long and the effect size was sufficiently large to suggest that at least part of the effect was drug related and not practice related. It has also been suggested that first-generation antipsychotics, particularly haloperidol, might attenuate the practice effect (23). However, this is not reported in the present study, since the cognitive improvement from a low dose of haloperidol was not significantly different from that of the second-generation antipsychotic drugs. Nevertheless, it is still conceivable that higher doses of haloperidol might exert a deleterious effect on cognitive performance (22). Furthermore, these data do not support the contention that treatment with haloperidol plus anticholinergic drugs is equivalent to treatment with second-generation antipsychotics.

There are several limitations to the present study. First, a more comprehensive cognitive battery might have revealed different results. However, there is little biological rationale to assume that a particular cognitive task not assessed in our study might have preferentially been affected by one but not another of the five drugs tested. Second, because of the open-label design and the possibility that some investigators might have been convinced by results of previous trials reporting advantages of second-generation antipsychotics over first-generation antipsychotics in terms of cognitive performance, this might have led to an "expectation bias," which could have conferred an advantage to the second-generation antipsychotic drugs over haloperidol (29). However, this potential bias is not supported by the results. Third, since antipsychotics can be detected in both blood and the CNS for many days and weeks after discontinuation of treatment, it is conceivable that the effect of the antipsychotic drugs administered before baseline testing could have affected baseline cognitive performance. In the present trial, like in many other similar trials (42), some patients had very brief washout periods, others had no wash-

TABLE 4. Cognitive Raw Scores at Baseline and 6-Month Follow-Up[a]

Task	Assessment			
	Baseline		6-Month Follow-Up	
	Mean	SD	Mean	SD
Trail Making Test Part A[b]	52.4	35.9	43.1	24.4
Trail Making Test Part B[b]	122.3	99.8	94.8	57.1
WAIS-III Digit Symbol	50.3	18.7	57.6	18.7
Purdue Pegboard Test	12.3	2.9	13.0	2.9
Rey Auditory Verbal Learning Test	42.9	11.5	48.4	10.9

[a] Patient:dropout ratio for each task is as follows: Trail Making Test Part A, 320:137; Trail Making Test Part B, 316:135; WAIS-III Digit Symbol, 316:131; Purdue Pegboard Test, 313:129; Rey Auditory Verbal Learning Test, 298:134.
[b] Lower scores are indicative of better performance.

TABLE 5. Relationship Between Cognitive Change and Clinical Change From Baseline

Item	Relationship to Change in PANSS Score at 6 Months (r)			
	Total	Positive	Negative	General
Composite score (change at 6-month follow-up)	–0.25[*]	–0.24[*]	–0.16[*]	–0.23[*]

[*] $p < 0.006$.

out period, and a few patients who could not be tested off medication because of the severity of their psychosis were allowed to have baseline testing shortly after random assignment. However, this is unlikely to have affected the results, since there were no baseline differences in cognitive performances among the five treatment groups, nor were there differences between the group of patients who were drug naive before baseline testing and the group of patients who received drugs before baseline testing. Furthermore, the NIMH Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Task Force on the design of clinical trials to assess the cognitive effects of drug treatment (43) and other similar trials evaluating cognition in first-episode patients (42) suggests that the interference of severe psychosis with testing might not justify antipsychotic washout. Finally, it cannot be ruled out that a first-generation antipsychotic drug or a second-generation antipsychotic drug not included in the present trial, such as risperidone or clozapine, would have proved to be superior to the drugs tested.

Despite the limitations of the present study, as well as other similar studies, it is unlikely that different trial designs or different patient populations would help differentiate any of the currently marketed antipsychotic drugs in terms of cognitive benefits. First, the discovery platform common to all antipsychotic drugs for the last 50 years has been the same, and its target has been the reduction of psychotic symptoms, not cognitive improvement. Antipsychotic drugs are screened based on their preclinical in vitro and in vivo similarities to other antipsychotics already proven to ameliorate psychosis in humans. The proof of concept and the go-/no-go decisions in phases II and III

clinical trials have been based on the antipsychotic properties of these drugs and not on their potential procognitive benefit. If second-generation antipsychotic drugs differ from first-generation antipsychotic drugs in areas other than adverse effect profile, they do so in terms of global effectiveness as reflected by the results of the trials conducted by Fleischhacker et al. (28) and Kahn et al. (29).

The present study, similar to many other previous studies, found only very weak correlations between psychotic symptoms at baseline or improvement in psychotic symptoms and cognitive impairment at baseline or improvement in cognitive performance, further underlying the separation between the desired procognitive and antipsychotic effects. It is therefore not surprising that not a single antipsychotic drug distinguishes itself in terms of cognitive benefits.

Interestingly, individual trials, even the most pragmatic and independently funded trials, very rarely provide definitive answers to the clinical question they intend to address. This is particularly true when the debate is about the advantages and distinguishing characteristics of drugs aimed at the same indications but perceived as older versus newer generations of drugs. Neither the CATIE study (44) nor the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (45–50), a trial showing very little differences between diuretics compared with novel antihypertensive drugs, settled the debate or immediately and radically affected prescribing practices. It appears that only a continuous stream of quality publications in high-impact journals and educational efforts can alter established perceptions and affect prescribing practices (51).

In summary, we found that antipsychotics, whether a low dose of haloperidol or several second-generation antipsychotics, were associated with improvement on cognitive test performance in patients in the early stages of schizophrenia but that the magnitude of improvement among these drugs did not differ.

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References

1. Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, Pappadopulos E, Willson DF, Alvir JM, Woerner MG, Geisler S, Kane JM, Lieberman JA: Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. Am J Psychiatry 2000; 157:549–559

2. Gold JM, Queern C, Iannone VN, Buchanan RW: Repeatable battery for the assessment of neuropsychological status as a screening test in schizophrenia, I: sensitivity, reliability, and validity. Am J Psychiatry 1999; 156:1944–1950

3. Heinrichs RW, Zakzanis KK: Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 1998; 12:426–445

4. Keefe RS, Eesley CE, Poe MP: Defining a cognitive function decrement in schizophrenia. Biol Psychiatry 2005; 57:688–691

5. Davidson M, Reichenberg A, Rabinowitz J, Weiser M, Kaplan Z, Mark M: Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. Am J Psychiatry 1999; 156:1328–1335

6. Fuller R, Nopoulos P, Arndt S, O'Leary D, Ho BC, Andreasen NC: Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. Am J Psychiatry 2002; 159: 1183–1189

7. Reichenberg A, Weiser M, Rapp MA, Rabinowitz J, Caspi A, Schmeidler J, Knobler HY, Lubin G, Nahon D, Harvey PD, Davidson M: Elaboration on premorbid intellectual performance in schizophrenia: premorbid intellectual decline and risk for schizophrenia. Arch Gen Psychiatry 2005; 62:1297–1304

8. Green MF: What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996; 153: 321–330

9. Harvey PD, Howanitz E, Parrella M, White L, Davidson M, Mohs RC, Hoblyn J, Davis KL: Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: a comparison across treatment sites. Am J Psychiatry 1998; 155:1080–1086

10. Davidson M, Keefe RS: Cognitive impairment as a target for pharmacological treatment in schizophrenia. Schizophr Res 1995; 17:123–129

11. Hyman SE, Fenton WS: Medicine: What are the right targets for psychopharmacology? Science 2003; 299:350–351

12. Mishara AL, Goldberg TE: A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. Biol Psychiatry 2004; 55:1013–1022

13. Woodward ND, Purdon SE, Meltzer HY, Zald DH: 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

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

15. Keefe RS, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, Lewine RR, Yurgelun-Todd DA, Gur RC, Tohen M, Tollefson GD, Sanger TM, Lieberman JA: Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am J Psychiatry 2004; 161:985–995

16. Keefe RS, Silva SG, Perkins DO, Lieberman JA: The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. Schizophr Bull 1999; 25:201–222

17. Vaiva G, Thomas P, Llorca PM, Dupont S, Cottencin O, Devos P, Mazas O, Rascle C, Steinling M, Goudemand M: SPECT imaging,

clinical features, and cognition before and after low doses of amisulpride in schizophrenic patients with the deficit syndrome. Psychiatry Res 2002; 115:37–48

18. Velligan DI, Newcomer J, Pultz J, Csernansky J, Hoff AL, Mahurin R, Miller AL: Does cognitive function improve with quetiapine in comparison to haloperidol? Schizophr Res 2002; 53:239–248

19. Velligan DI, Prihoda TJ, Sui D, Ritch JL, Maples N, Miller AL: The effectiveness of quetiapine versus conventional antipsychotics in improving cognitive and functional outcomes in standard treatment settings. J Clin Psychiatry 2003; 64:524–531

20. Wagner M, Quednow BB, Westheide J, Schlaepfer TE, Maier W, Kuhn KU: Cognitive improvement in schizophrenic patients does not require a serotonergic mechanism: randomized controlled trial of olanzapine vs amisulpride. Neuropsychopharmacology 2005; 30:381–390

21. Woodward ND, Purdon SE, Meltzer HY, Zald DH: A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. Int J Neuropsychopharmacol 2005; 8:457–472

22. Carpenter WT, Gold JM: Another view of therapy for cognition in schizophrenia. Biol Psychiatry 2002; 51:969–971

23. Goldberg TE, Goldman RS, Burdick KE, Malhotra AK, Lencz T, Patel RC, Woerner MG, Schooler NR, Kane JM, Robinson DG: 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

24. Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S: Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am J Psychiatry 2006; 163:185–194

25. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209–1223

26. Keefe RS, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, Meltzer HY, Green MF, Capuano G, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Davis CE, Hsiao JK, Lieberman JA, CATIE Investigators; Neurocognitive Working Group: Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. Arch Gen Psychiatry 2007; 64:633–647

27. Sweet RA, Pollock BG, Mulsant BH, Rosen J, Sorisio D, Kirshner M, Henteleff R, DeMichele MA: Pharmacologic profile of perphenazine's metabolites. J Clin Psychopharmacol 2000; 20: 181–187

28. Fleischhacker WW, Keet IP, Kahn RS: The European First Episode Schizophrenia Trial (EUFEST): rationale and design of the trial. Schizophr Res 2005; 78:147–156

29. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, Gheorghe MD, Rybakowski JK, Galderisi S, Libiger J, Hummer M, Dollfus S, López-Ibor JJ, Hranov LG, Gaebel W, Peuskens J, Lindefors N, Riecher-Rössler A, Grobbee DE; EUFEST Study Group: Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 2008; 371:1085–1097

30. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Herqueta T, Baker R, Dunbar GC: The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59(suppl 20):22–33; quiz 34–57

31. Kay SR, Fiszbein A, Opler LA: The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261–276

32. Leucht S, Engel RR: The relative sensitivity of the Clinical Global Impression Scale and the Brief Psychiatric Rating Scale in antipsychotic drug trials. Neuropsychopharmacology 2006; 31: 406–412

33. Gerlach J, Korsgaard S, Clemmesen P, Lauersen AM, Magelund G, Noring U, Povlsen UJ, Bech P, Casey DE: The St Hans Rating Scale for extrapyramidal syndromes: reliability and validity. Acta Psychiatr Scand 1993; 87:244–252

34. Rey A: L'Examen clinique en psychologie. Paris, Presses Universitaires de France, 1964

35. Reitan RM, Wolfson D: The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation, 2nd ed. Tucson, Ariz, Neuropsychology Press, 1993

36. Costa LD, Vaughan HG Jr, Levita E, Farber N: Purdue Pegboard as a predictor of the presence and laterality of cerebral lesions. J Consult Psychol 1963; 27:133–137

37. Wechsler D: Wechsler Adult Intelligence Scale–3rd Edition. San Antonio, Tex, Psychological Corporation, 1997

38. Cohen J: Statistical power analysis for the behavioral sciences. Mahwah, NJ, Lawrence Erlbaum Associates, 1988

39. Harvey PD, Rabinowitz J, Eerdekens M, Davidson M: Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. Am J Psychiatry 2005; 162:1888–1895

40. Keefe RS, Sweeney JA, Gu H, Hamer RM, Perkins DO, McEvoy JP, Lieberman JA: Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. Am J Psychiatry 2007; 164:1061–1071

41. Keefe RS, Malhotra AK, Meltzer HY, Kane JM, Buchanan RW, Murthy A, Sovel M, Li C, Goldman R: Efficacy and safety of donepezil in patients with schizophrenia or schizoaffective disorder: significant placebo/practice effects in a 12-week, randomized, double-blind, placebo-controlled trial. Neuropsychopharmacology 2008; 33:1217–1228

42. Hill SK, Schuepbach D, Herbener ES, Keshavan MS, Sweeney JA: Pretreatment and longitudinal studies of neuropsychological deficits in antipsychotic-naive patients with schizophrenia. Schizophr Res 2004; 68:49–63

43. Buchanan RW, Davis M, Goff D, Green MF, Keefe RS, Leon AC, Nuechterlein KH, Laughren T, Levin R, Stover E, Fenton W, Marder SR: A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. Schizophr Bull 2005; 31:5–19

44. Cascade EF, Kalali AH, Lieberman J, Hsiao J, Keefe R, Stroup S: Use of antipsychotics pre- and post-dissemination of CATIE data. Psychiatry 2007; 4:21–23

45. Furberg CD, Hall MA, Sevick MA: Balancing commercial and public interests. Curr Control Trials Cardiovasc Med 2004; 5:6

46. Lasaridis AN, Sarafidis PA: What lies behind the intense criticism of ALLHAT? J Hypertens 2004; 22:223–224; author reply 224–227

47. Leenen FH: ALLHAT: What has it taught us so far? CMAJ 2004; 171:719–720

48. Moser M, Oparil S, Cushman W, Papademetriou V: The ALLHAT study revisited: Do newer data from this trial and others indicate changes in treatment guidelines? J Clin Hypertens (Greenwich) 2007; 9:372–380

49. Sawicki PT, McGauran N: Have ALLHAT, ANBP2, ASCOT-BPLA, and so forth improved our knowledge about better hypertension care? Hypertension 2006; 48:1–7

50. Aleman A, Kahn RS, Selten JP: Sex differences in the risk of schizophrenia: evidence from meta-analysis. Arch Gen Psychiatry 2003; 60:565–571

51. National Institutes of Health: Landmark Hypertension Treatment Study Launches Extensive Physician and Patient Education Program to Improve Public Health. Bethesda, Md, NIH, 2006