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Cognitive Improvement in Schizophrenic Patients does not Require a Serotonergic Mechanism: Randomized Controlled Trial of Olanzapine *vs* Amisulpride

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Combined serotonin-2A (5-HT_{2A}) and dopamine-2 (D_2) receptor blockade has been proposed as a candidate mechanism by which second-generation antipsychotics (SGAs) improve both cognition and negative symptoms in schizophrenic patients, in contrast to antipsychotics of the first generation. The SGA amisulpride, however, only binds to D_2/D_3 receptors, which makes it an interesting tool to test this assumption. In a randomized controlled trial, 52 schizophrenic patients were allocated to treatment with either olanzapine (10–20 mg/day) or amisulpride (400–800 mg/day). A comprehensive neuropsychological test battery and clinical ratings were used to assess participants at inclusion and after 4 and 8 weeks. Cognitive improvements of moderate size were observed, with effect sizes similar to those obtained in previous studies on the cognitive effects of SGAs. Importantly, amisulpride was not inferior to olanzapine for any cognitive domain. Combined 5-HT_{2A}/D_2 receptor blockade is probably not necessary for cognitive improvement by SGAs.
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INTRODUCTION

The advent of novel antipsychotic medications like amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, remoxipiride, risperidone, sertindole, ziprasidone, and zotepine represents an important improvement in the treatment of schizophrenia. Among the advantages of these 'second-generation' antipsychotics (SGAs) (also referred to as 'atypical' or 'modern' antipsychotics) over 'first-generation' antipsychotics (FGAs) (also referred to as 'typical', 'traditional', or 'conventional' antipsychotics) are reduced extrapyramidal side effect profiles (Rosenheck *et al*, 1997; Simpson and Lindenmayer, 1997), reduced risk for tardive dyskinesia (Chouinard, 1995; Lieberman *et al*, 1994), greater effects on the negative and positive symptoms (Kane *et al*, 1988; Marder and Meibach, 1994; Beasley *et al*, 1996), and possibly beneficial effects on cognitive functioning (Purdon *et al*, 2000; Harvey *et al*, 2003; Bilder *et al*, 2002). SGAs have diverse receptor profiles, and the mechanism of action is still controversial (Seeman, 2002). The antagonism of SGAs to serotonin-2A (5-HT_{2A}) receptors has been invoked to explain the improved efficacy of SGAs as compared to FGAs (with which they share the dopamine (D) antagonism), because most SGAs have a greater difference between 5-HT_2 and D_2 affinity than FGAs (Meltzer *et al*, 1989; Ichikawa and Meltzer, 1999; Meltzer, 1999). This view is supported by the fact that SGAs can increase cortical dopamine by 5-HT_{2A} blockade in the rat (Liegeois *et al*, 2002). Furthermore, the role of 5-HT_{2A} receptors in modulating working memory in humans has been established (Luciana *et al*, 1998; Williams *et al*, 2002).

Since the introduction of SGAs, treatment success is not only defined by effects on positive and negative symptoms, but also by improvements in domains of cognitive functions, which are highly relevant for functional outcome (Liddle, 2000; Sharma and Mockler, 1998; Sharma and Antonova, 2003). Several studies reported improvements after switching patients from FGAs to risperidone and clozapine (Keefe *et al*, 1999). In early randomized controlled trials, risperidone was found to be superior to haloperidol with regard to verbal working memory (Green *et al*, 1997) and verbal declarative memory (Kern *et al*, 1999). A randomized clinical trial of Purdon *et al* (2000) compared cognitive effects of haloperidol with two SGAs (olanzapine and risperidone) over 12 months and found olanzapine to be superior to risperidone and haloperidol in

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a global cognitive measure, with few reliable treatment differences for single tests or cognitive domains. This study has been criticized for high dropout rates, which were different between treatments (Weiss *et al*, 2002), and for a high average dosage of risperidone (Sharma, 2002). A subsequent 14-week study by Bilder *et al* (2002) confirmed that 10–40 mg olanzapine was superior to 10–30 mg haloperidol (particularly with regard to attention), but also found improvements in memory, which were most marked for 4–16 mg risperidone, implicating that different SGAs may differ in their patterns of cognitive effects. However, a large study of Harvey *et al* (2003), comparing the cognitive effects of 5–20 mg olanzapine or 2–6 mg/day risperidone over 8 weeks in 377 patients, found no differences between both treatments, while performance of all patients improved for several domains. Similarly, in a recent 6-week head to head study, Harvey *et al* (2004) demonstrated identical positive effects of ziprasidone and olanzapine on many cognitive functions. In order to assess the comparative neurocognitive effectiveness of several SGAs (olanzapine, quetiapine, risperidone, ziprasidone) in large samples, the NIMH has funded the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE; Keefe *et al*, 2003).

The available body of data is encouraging because many commonly prescribed SGAs seem to improve cognitive functioning reliably, albeit modestly. However, from a theoretical point of view, the cognitive equivalence of SGAs evident from large trials is somewhat disappointing, because the pharmacological differences between the SGAs tested so far do not result in different cognitive effects, and therefore the mode (or the modes) of action of SGAs on cognition remains unclear: 'Whether relatively more potent 5-HT_{2A} receptor compared to D_2 antagonism has a major or, indeed any role in the cognitive effects of these agents is not known' (Meltzer, 2002, p 824).

In order to test critically the supposed crucial role of 5-HT_{2A} antagonism for cognitive improvement, an examination of substances that lack this 5-HT_{2A} mechanism but that qualify as a SGA because of their clinical profile would be most informative. Fortunately, there is a SGA, approved for the treatment of schizophrenia in Europe and Canada, that can be used as a tool for testing the necessity of a 5-HT_{2A} antagonism for cognitive change. Amisulpride is a pure D_2/D_3 receptor antagonist. However, amisulpride has not been compared with other SGAs having a 5-HT_{2A} antagonism with regard to cognitive functions to date.

Aside from their putative effects on cognition, SGAs have clearly stronger effects on negative symptoms than FGAs, and the combined 5-HT_{2A}/D_2 antagonism, which might explain cognitive effects of SGAs, is also been considered to explain this superiority (Meltzer, 2002). However, a meta-analysis of Leucht *et al* (2002) showed that amisulpride was superior to FGA or placebo in improving primary negative symptoms, casting some doubt on the 'combined antagonism' notion. Negative symptoms often go together with cognitive dysfunction (Berman *et al*, 1997; Brebion *et al*, 2000), and negative symptom scales contain several items for the clinical assessment of cognition, like attention, abstraction, and insight. If the combined 5-HT_{2A}/D_2 antagonism is not necessary for the improvement of negative symptoms, as the meta-analysis of Leucht *et al* (2002) suggests, it may also not be relevant for the improvement of cognitive deficits.

In summary, recent data from well-designed studies show that several SGAs all sharing a serotonergic component improve cognitive functioning in schizophrenic patients. One prominent theory, mainly supported by animal data, proposes that SGAs increase cortical dopamine partly because of their ability to block potently serotonin 5-HT_{2A} receptors (Liegeois *et al*, 2002; Meltzer and Sumiyoshi, 2003).

The present study was designed to compare directly two pharmacologically very distinct antipsychotic drugs, olanzapine and amisulpride, with regard to negative symptoms and cognitive deficits, and to test whether different mechanisms of action might underlie similar clinical efficacy. Thus, we tested the hypothesis that serotonergic action is the common and necessary mode of action of all antipsychotic medications with beneficial effects on negative symptoms and cognition.

METHODS

Participants

Patients admitted to the Psychiatric Hospital of the University of Bonn for in-patient treatment were considered eligible for the study if the following criteria were met: a diagnosis of schizophrenia according to DSM IV and ICD 10, age 18–65, Clinical Global Impressions (CGI) = 4 or more, Positive and Negative Symptom Scale (PANSS) = 61 or more, and no clozapine treatment within 3 months prior to inclusion. Furthermore, subjects were excluded if they had any history of CNS trauma, epilepsy, meningoencephalitis; instable somatic condition; substance dependency; lack of sufficient contraception in premenopausal females; history of antipsychotic drug resistance; and risk of suicide or aggressive behavior.

A total of 52 patients meeting these criteria were randomly allocated to treatment with either olanzapine (10–20 mg) or amisulpride (400–800 mg). Randomization was performed by distributing the study medications to containers according to a pseudo-random computer algorithm.

Prior to inclusion, 12 patients (eight in the amisulpride group, four in the olanzapine group) were treated with FGAs and three (all in the olanzapine group) with SGAs (two risperidone, one quetiapine). A total of 21 patients were antipsychotically untreated at least for 4 weeks prior to inclusion. Prior to inclusion, two patients (one amisulpride, one olanzapine) were treated with selective serotonin reuptake inhibitors (SSRIs) citalopram or sertraline, which was stopped 2 days prior to inclusion. Previous oral psychotropic medication was stopped 2 days prior to inclusion and treatment with depot antipsychotics was stopped at least two biological half-lifes prior to inclusion.

The study was approved by the institutional review board of the University of Bonn Medical School. All participants gave written informed consent before inclusion.

Treatments

After a wash-out phase of 2 days, in which only lorazepam up to 4 mg daily was permitted, participants received, according to randomization, a half-flexible dose range of 10–20 mg olanzapine or 400–800 mg amisulpride. Psychiatrists and patients were blinded to treatment group and prescribed levels of medication, starting with either 10 mg olanzapine or 400 mg amisulpride at day 1. According to clinical response, the dosage was adjusted within the first 3 days in the range defined above. The following other pharmacological treatments only were permitted: (1) up to 4 mg lorazepam per day for treatment of agitation, (2) adjunct treatment with zopiclone up to 22.5 mg daily, and (3) up to 4 mg of biperiden for treatment of extrapyramidal motor symptoms (EPMS). However, lorazepam, zopiclone, and biperiden were tapered 24 h before each neuropsychological testing.

Clinical Assessment

Blind raters performed all clinical symptom ratings with PANSS (Kay *et al*, 1992), Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983), Simpson–Angus Scale (SAS; Simpson and Angus, 1979), and CGI (Guy, 1976) at inclusion (week 0) and after 1, 4, and 8 weeks.

Neurocognitive Assessment

The cognitive assessment was designed to cover a range of reliable and validated tests frequently used in similar studies. We attempted to balance the interest for a broad assessment of important cognitive domains with load on patients in order to reduce the possibility of attrition. The battery took about 90–120 min including breaks as needed, and was generally well tolerated by patients. The tests were grouped into four cognitive domains (attention, executive functions, working memory, and verbal learning and memory) according to *a priori* considerations. In addition, a global cognitive index was constructed by summing and averaging across the *z*-scored variables of neurocognitive tests.

The test battery was administered three times, the first time within the first week after randomization and start of treatment with olanzapine or amisulpride, the second time after 4 weeks, and the last time after 8 weeks (at the end of treatment). Since patients were acutely ill and required inpatient treatment, an assessment prior to antipsychotic medication was not performed, in order to establish cooperation of patients and thus to ensure reliable test performance.

Attention. We used the *trail-making test A* (TMT-A) to assess visomotor speed (Reitan and Wolfson, 1993). The dependent variable was the time required to complete the test. To assess vigilance, we used the identical pairs version of the *continuous performance test* (CPT-IP) (Cornblatt *et al*, 1988). The signal detection index d-prime and the reaction time to hits were the dependent variables.

Executive functions. The second part of the *trail-making test* (TMT-B) evaluated both visomotor speed and the ability to alternate between sets. The dependent variable was the time required to complete the test. To assess global verbal fluency, we administered three fluency tests: *category and letter fluency* (Spreen and Strauss, 1998) as well as *action (verb naming) fluency* (Piatt *et al*, 1999). The respective fluency scores were summed to a global fluency score, which was the dependent variable. We also administered the *maze test* to assess problem solving and higher cognitive functioning (Chapuis, 1959). The time required to complete the test and the sum of errors were the dependent variables.

Working memory. The *letter-number sequencing task* was used to measure verbal working memory (Wechsler, 1997). The sum of correct trials was the dependent variable. The first trial of the German version of the *Rey auditory verbal learning test* was also used as a measure for verbal working memory (Helmstaedter *et al*, 2001). The number of correct words was the dependent variable. To evaluate spatial working memory, we used the *one-point test*, delayed recall (Keefe *et al*, 1995). The dependent variable was the mean deviation from the shown points in millimeters. A further measure of visual working memory was assessed with the nonverbal part of the *self-ordered pointing task* (SOPT; Petrides and Milner, 1982). The sum of errors was the dependent variable.

Verbal learning and memory. To assess verbal declarative memory function, we administered the *Rey auditory verbal learning test*. The sum of words of trials 2–5, the delayed recall trial, and the recognition score $p(A)$ (Forrester and Geffen, 1991) were the dependent variables. In addition, we assessed story recall with the *logical memory task* of the German version of the *Rivermead behavioural memory test* (Wilson *et al*, 1992). The number of recalled cues was the dependent variable.

With the exception of CPT-IP, the one-point test, and SOPT, we used three different parallel versions of the neurocognitive tests at the three test sessions.

Data Analysis

Before analysis of clinical and neuropsychological data, we examined demographic variables and severity of illness as well as test performance at inclusion in the patients who completed neuropsychological testing at least at week 4 compared with those who did not. All clinical and neurocognitive variables were analyzed by *t*-tests to determine whether baseline differences existed between treatment groups.

A total of 17 variables were extracted from the neuropsychological tests for each test session. The neuropsychological data of the patients were standardized with reference to the mean and standard deviation of the entire sample. Signs were adjusted so that negative values reflect impairment. The common *z*-metric also allows for an integration of single variables into cognitive domains and into a global cognitive index, which was used as a primary measure for confirmatory testing. We used the *last*

observation carried forward (LOCF) method; thus, measures of patients who dropped out after week 4 were carried on with their last clinical and neuropsychological scores to week 8.

Negative symptoms and cognitive functioning constituted the main outcomes. Analysis of treatment effects in clinical scales used the general linear models approach to repeated measures analysis of variance (SPSS Inc., Chicago, Illinois) with week 0, 1, 4, and 8 (end point) scores as dependent variables, time as a within-subject repeated measure (four-fold), and treatment group (amisulpride, olanzapine) as a between-subjects fixed factor (two-fold). Analysis of treatment effects in each cognitive domain and the global index used the general linear models approach to repeated measures analysis of variance with week 1, 4, and 8 (end point) scores as dependent variables, time as a within-subject repeated measure (three-fold), and treatment group (amisulpride, olanzapine) as a between-subjects fixed factor (two-fold). Frequency data (gender, dropout rates) were analyzed by χ^2 tests. Inter-relations between cognitive and clinical improvement were tested by Pearson's product-moment correlation. The confirmatory statistical comparisons of all data were carried out at a significance level set at $P = 0.05$ (two-tailed).

Individual test scores were not analyzed separately, since with 17 tests we felt the analysis would suffer either from capitalization on chance (given the number of tests) or from overly conservative alpha levels that would be needed to correct for test multiplicity.

RESULTS

Demographic Data

Groups of patients randomized to receive either treatment did not differ with regard to proportion of male and female subjects, age, age of illness onset, number of previous episodes, years of education, or number of weeks in study. This was true for the full sample ($N = 26$ in each treatment group) as well as for the sample with neuropsychological data at least for weeks 1 and 4 ($N = 18$ in each treatment group) (Table 1).

Table 1 Demographic and Some Clinical Characteristics of Patients with Schizophrenia Randomly Assigned to Receive Amisulpride or Olanzapine (Means and Standard Deviations in Parentheses; Sex in Frequency Data)

	Amisulpride ($n = 18$)	**Olanzapine ($n = 18$)**
Age	38.3 (8.7)	34.3 (7.3)
Sex (females/males)	8/10	5/13
Years of education	13.6 (2.4)	14.3 (3.7)
Age of onset	28.4 (7.6)	27.3 (7.0)
Duration of illness (years)	9.8 (11.2)	7.0 (6.7)
Number of episodes	3.1 (1.7)	2.8 (2.4)
Number of weeks in study	7.3 (1.3)	6.9 (1.8)
Dose at end point (mg/day)	511.1 (171.1)	15.0 (4.5)

Dropouts

A total of 52 patients were randomized. Two patients withdrew informed consent in the first week (amisulpride/olanzapine: 1/1). In all, 13 patients dropped out between weeks 1 and 4: two because of noncompliance (1/1), three were lost to follow-up (2/1), three were lost because of a lack of treatment efficacy (1/2), one turned out as slightly mentally retarded in the first neuropsychological test session (0/1), and four showed adverse events (amisulpride: one exanthema and one EPMS; olanzapine: one sedation and one increase of transaminases). A total of 10 patients dropped out between weeks 4 and 8: four were noncompliant (2/2), three were lost to follow-up (1/2), two showed adverse events (amisulpride: one galactorrhea; olanzapine: one sedation), and one was lost because of a lack of treatment efficacy (1/0). One further patient could not complete the neuropsychological assessment at weeks 4 and 8 and was therefore excluded from data analysis. Dropout rates in both treatment groups did not differ in χ^2 tests. Patients who completed the study (at least until week 4) and patients who dropped out before week 4 did not differ at inclusion in psychopathology and cognition measures.

Psychopathology

At inclusion, both treatment groups did not differ significantly in any psychopathological scale. Analysis of variance (time × group, with repeated measures at factor time (four-fold, CGI item 2 three-fold)) showed a significant main effect of factor time in all scales and subscales, reflecting strong improvement of psychiatric symptoms (PANSS total: $F(3/102) = 80.9$, $P < 0.001$; SANS total: $F(3/102) = 24.8$, $P < 0.001$; CGI item 1: $F(3/102) = 70.4$, $P < 0.001$). No significant interactions of factor time and group occurred, but there were two trends of interaction in the PANSS general scale ($F(3/102) = 2.4$, $P = 0.08$) and SANS Affective Flattening scale ($F(3/102) = 2.0$, $P = 0.12$). The amisulpride group tended to show a stronger reduction of symptoms in these scales. Analysis of variance (with repeated measures at factor time) within each group showed a significant decrease of psychiatric symptoms in all scales and subscales in both groups with the exception of the SANS Affective Flattening scale where the improvement was not significant in the olanzapine group. Figures 1 and 2 show the development of psychiatric symptoms in PANSS and SANS across treatment period. The mean ($\pm$standard deviation) CGI item 1 (severity) scores (amisulpride/olanzapine) were for inclusion $6.1 \pm 0.7/6.2 \pm 0.4$, for week 1 $5.3 \pm 0.8/5.4 \pm 1.1$, for week 4 $3.9 \pm 1.0/4.4 \pm 0.9$, and for the end point $3.7 \pm 1.0/4.3 \pm 1.1$. The CGI item 2 (change) scores were for week 1 $3.6 \pm 0.6/4.0 \pm 1.1$, for week 4 $3.1 \pm 1.0/3.3 \pm 0.8$, and for the end point $2.7 \pm 1.1/3.1 \pm 1.0$.

Neurological Symptoms

At inclusion, both treatment groups did not differ with regard to EPMS (measured with SAS). Analysis of variance (time × group, with repeated measures at factor time (four-fold)) showed no significant main or interaction effects. At the end of study, the amisulpride group showed slightly

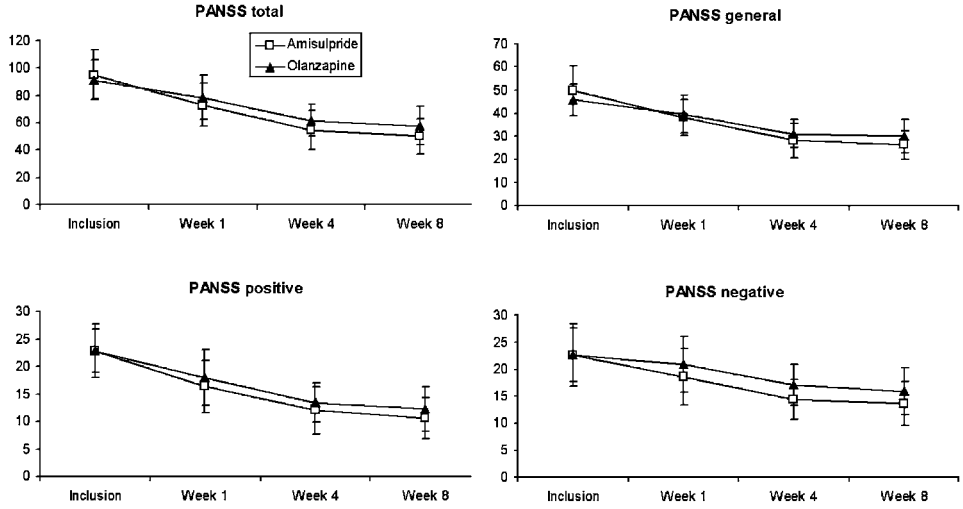

Figure 1 PANSS at inclusion and at weeks 1, 4, and 8 (end point) for patients with schizophrenia randomly assigned to receive amisulpride or olanzapine (LOCF, means and standard deviations).

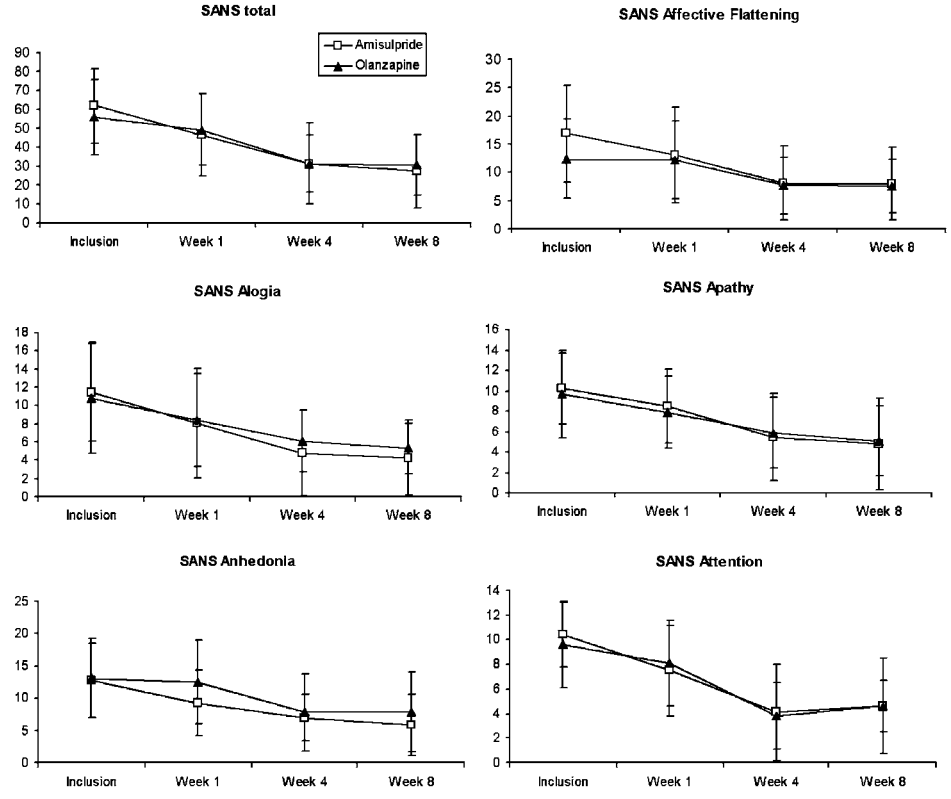

Figure 2 SANS at inclusion and at weeks 1, 4, and 8 (end point) for patients with schizophrenia randomly assigned to receive amisulpride or olanzapine (LOCF, means and standard deviations).

more EPMS, but this difference was not statistically significant (Figure 3).

Cognition

At inclusion (week 1), the treatment groups did not differ significantly in the global cognition index, which summarizes the performance of all neuropsychological tests. Analysis of variance (time × group, with repeated measures at factor time (three-fold)) showed a significant main effect of factor time ($F(2/68) = 10.0$, $P < 0.001$), but no significant interaction of both factors. Thus, both groups showed comparable and significant improvement of global cognitive functioning (see Table 2).

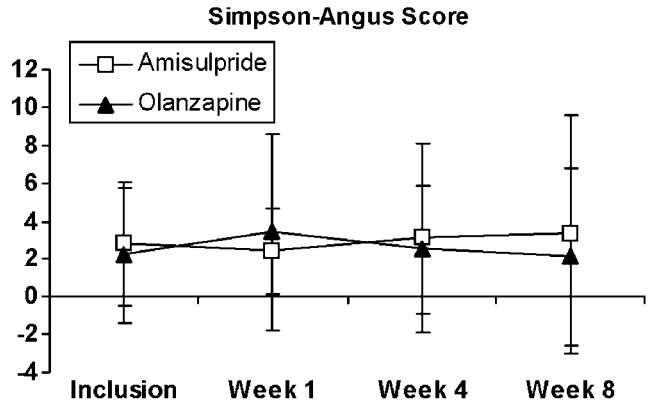

Figure 3 SAS at inclusion and at weeks 1, 4, and 8 (end point) for patients with schizophrenia randomly assigned to receive amisulpride or olanzapine (LOCF, means and standard deviations).

For cognitive domains (attention, executive functions, working memory, and declarative memory), the pattern was similar: at week 1, both groups did not differ significantly in any domain. Analyses of variance (time × group, with repeated measures at factor time (three-fold)) showed a significant main effect of factor time in executive functions ($F(2/68) = 4.9$, $P < 0.01$), working memory ($F(2/68) = 14.0$, $P < 0.001$), and declarative memory ($F(2/68) = 4.6$, $P < 0.05$), but not in attention ($F(2/68) = 1.4$, $P = 0.25$). No significant interactions of both factors occurred, but in attention there was a weak trend ($F(2/68) = 2.1$, $P = 0.13$) for an interaction of factors group and time, reflecting a stronger increase of attention performance in the amisulpride group. Otherwise, both groups showed comparable and significant improvement of executive functions, working memory, and declarative memory.

Analyses of variance (with repeated measures at factor time (three-fold)) within each treatment group showed a more differentiated pattern: the amisulpride group showed a significant main effect of factor time in the domains attention ($F(2/34) = 5.1$, $P < 0.01$), executive functions ($F(2/34) = 7.8$, $P < 0.01$), and working memory ($F(2/34) = 5.0$, $P < 0.01$), as well as in the global cognitive index ($F(2/34) = 13.4$, $P < 0.001$). The domain declarative memory showed a trend for a main effect in this factor ($F(2/34) = 2.7$, $P = 0.08$). The olanzapine group showed a significant main effect of factor time only in the domain working memory ($F(2/34) = 9.3$, $P < 0.001$), and trends for a main effect in this factor for declarative memory ($F(2/34) = 2.0$, $P = 0.15$) as well as for the global cognitive index ($F(2/34) = 2.5$, $P = 0.10$). Since overall ANOVA (including both treatment groups) did not result in a significant group × time interaction, these results from the within-group analyses have to be interpreted with caution, but they might indicate that amisulpride had a broader range of cognitive effects.

In order to compare the effect sizes of this study with those of other studies, effect sizes for improvement were calculated for patients by dividing the amount of improvement (*z*-score at end point (LOCF) minus *z*-core at week 1) by the standard deviation of all patients at week 0. This was carried out for each cognitive domain and for the global cognitive index. The effect sizes were 0.30 for the global cognitive index (amisulpride/olanzapine: 0.40/0.20), 0.25 for attention (0.57/−0.05), 0.30 for executive functions (0.42/0.18), 0.34 for working memory (0.28/0.39), and 0.14 for declarative memory (0.19/0.08).

Relationship of Cognitive Improvements to Change of Negative and Positive Symptoms

To examine which cognitive improvements were accompanied by symptomatic change, correlations between change scores of the cognitive domain measures and the reduction of negative and positive symptoms were calculated. Improvement of the PANSS positive subscale was neither correlated with improvement of the global cognitive index nor with improvements of any cognitive domain. In contrast, the improvement of the PANSS negative subscale ($r = -0.40$, $P < 0.05$) and of the SANS total score ($r = -0.47$, $P < 0.01$) showed moderate but significant associations with improvements of the global cognitive index. Furthermore, improvement of the global cognitive index was significantly correlated with improvement of the PANSS general subscale ($r = -0.37$, $P < 0.05$), SANS Affective Flattening ($r = -0.45$, $P < 0.01$), SANS Apathy ($r = -0.49$, $P < 0.01$), SANS Anhedonia ($r = -0.49$, $P < 0.01$), PANSS total score ($r = -0.38$, $P < 0.05$), CGI-Severity ($r = -0.51$, $P < 0.01$), and SAS ($r = -0.40$, $P < 0.05$). Improvement of attention was significantly correlated with improvement of CGI-Severity ($r = -0.39$, $P < 0.05$), SANS total ($r = -0.38$, $P < 0.05$), and SANS Affective Flattening ($r = -0.49$, $P < 0.01$). Improvement of executive functions was significantly correlated with improvement of SANS Apathy ($r = -0.35$, $P < 0.05$). Improvement of working memory was significantly correlated with improvement of CGI-Severity ($r = -0.48$, $P < 0.01$), SANS Apathy ($r = -0.38$, $P < 0.05$), and SANS Anhedonia ($r = -0.36$, $P < 0.05$). Improvement of declarative memory was significantly correlated with improvement of SAS ($r = -0.37$, $P < 0.05$).

DISCUSSION

Both olanzapine and amisulpride proved to be well effective in alleviating both negative and positive symptoms, with no indication of differential effects in any of the rating scales. The consideration of the mean scores (regardless of statistical significance) gives no indication of superior efficacy of olanzapine. The equivalence of olanzapine and amisulpride with regard to positive and negative symptoms has also been demonstrated in another randomized comparison study with 377 acutely psychotic schizophrenic patients, where 2 months after treatment onset no differences in BPRS total or BPRS factor scores, or depressive symptoms (Martin *et al*, 2002) were evident. A meta-analysis by Davis *et al* (2003) indicated that olanzapine and amisulpride are both equally superior to conventional antipsychotics regarding PANSS or BPRS total scores (effect sizes, olanzapine, $d = 0.21$, amisulpride, $d = 0.29$). The effectiveness of amisulpride on negative symptoms was also confirmed by a meta-analysis of Leucht *et al* (2002). In line with much other evidence, the present study suggests that olanzapine and amisulpride exert highly similar effects

Table 2 Neurocognitive Global and Domain *z*-Scores and Scores on Individual Neuropsychological Tests at Weeks 1, 4, and 8 (End Point)

	Amisulpride ($n = 18$)			Olanzapine ($n = 18$)		
	Week 1	Week 4	Week 8	Week 1	Week 4	Week 8
Measure	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Global cognitive index	0.06 (0.47)	0.28 (0.48)	0.30** (0.47)	−0.06 (0.72)	0.14 (0.52)	0.06‡ (0.49)
Neurocognitive domain scores						
Attention	−0.05 (0.53)	0.20 (0.57)	0.29** (0.56)	0.05 (0.67)	0.01 (0.47)	0.02 (0.44)
Executive functions	0.02 (0.56)	0.14 (0.48)	0.30** (0.40)	−0.02 (0.76)	0.17 (0.43)	0.10 (0.66)
Working memory	0.14 (0.62)	0.40 (0.58)	0.37** (0.57)	−0.14 (0.99)	0.23 (0.73)	0.18** (0.69)
Declarative memory	0.11 (0.62)	0.39 (0.74)	0.25‡ (0.76)	−0.11 (0.85)	0.14 (0.98)	−0.05 (0.94)
Neuropsychological test scores						
Attention						
Trail-making test A (s)	43.3 (20.2)	33.8 (14.1)	34.1 (18.3)	44.9 (35.6)	35.8 (13.1)	34.9 (14.0)
CPT-IP, reaction time hits (ms)	550.8 (72.28)	570.9 (70.9)	541.1 (70.0)	546.0 (112.2)	580.5 (67.8)	581.5 (79.7)
CPT-IP, d-prime	0.69 (0.62)	1.02 (0.66)	0.99 (0.88)	0.84 (0.45)	0.80 (0.52)	0.81 (0.45)
Executive functions						
Trail-making test B (s)	92.9 (45.9)	90.4 (31.7)	79.2 (32.1)	127.4 (106.7)	111.2 (54.3)	100.2 (55.7)
Labyrinth tests 1–3, time total (s)	113.2 (59.0)	65.6 (40.1)	68.7 (24.9)	104.1 (85.2)	65.3 (47.9)	109.1 (107.95)
Labyrinth tests 1–3, errors total	15.8 (9.1)	15.4 (8.0)	12.5 (8.7)	16.6 (9.0)	14.4 (7.7)	14.1 (7.3)
Fluency total (verb naming, letter, category) (words)	27.1 (10.0)	29.2 (10.3)	28.8 (11.2)	30.2 (10.3)	31.0 (9.4)	30.0 (9.5)
Working memory						
Letter-number sequencing (trials)	12.6 (3.5)	12.7 (3.6)	13.5 (3.4)	13.6 (4.4)	13.6 (4.0)	13.6 (6.8)
One-point test delayed (mm)	262.1 (83.4)	278.4 (100.2)	266.9 (103.2)	478.3 (407.1)	327.0 (133.5)	341.6 (138.0)
Subject ordered pointing task figures, errors	12.0 (6.0)	9.4 (5.4)	9.9 (6.2)	13.6 (6.8)	12.0 (5.7)	11.7 (6.2)
Auditory verbal learning task first trial (words)	5.2 (1.8)	6.4 (1.7)	5.8 (1.6)	5.2 (2.3)	5.7 (2.3)	5.3 (1.7)
Declarative memory						
Auditory verbal learning task sum of trials 2–5 (words)	39.4 (8.6)	41.0 (9.8)	38.8 (9.8)	36.9 (10.7)	37.3 (12.3)	36.7 (12.5)
Auditory verbal learning task delayed recall 30 min (words)	7.6 (3.2)	8.1 (3.5)	8.1 (3.8)	7.5 (3.7)	7.6 (4.7)	6.3 (3.9)
Auditory verbal learning task recognition, *p*(*A*)	0.68 (0.19)	0.76 (0.16)	0.69 (0.15)	0.68 (0.21)	0.68 (0.17)	0.61 (0.16)
Logical memories recalled cues	5.9 (2.5)	6.8 (2.32)	7.0 (2.4)	4.3 (2.7)	6.7 (3.1)	6.7 (3.5)

Only the global cognitive index and the neurocognitive domain scores were analyzed statistically. The interaction of treatment × time was not significant for any of these scores. The symbols after the *z*-scores for week 8 indicate statistical significance of change within each treatment group across 8 weeks. ‡$P<0.1$, **$P<0.01$.

on positive as well as negative symptoms, despite the fact that amisulpride lacks the 5-HT_{2A} component. This is difficult to reconcile with the hypothesis that a serotonergic action is necessary to improve negative symptoms in schizophrenic patients (Meltzer *et al*, 1989; Ichikawa and Meltzer, 1999; Meltzer, 1999).

The present study is the first one directly comparing the cognitive benefits of olanzapine and amisulpride. In both treatment groups, statistically significant improvements occurred during treatment, which were comparable in effect size to the improvements noted in other studies (Harvey and Keefe, 2001). However, neither for the primary outcome measure (global cognitive index) nor for any of the four cognitive domain measures, a significant difference between both antipsychotics could be demonstrated. Exploratory data analysis for single tests revealed possibly stronger effects for olanzapine on working memory, and possibly stronger effects of amisulpride on attention and executive functioning. These effects may deserve further examination in future studies.

One limitation of the present study is its limited power to detect superiority. Since the effect size in favor of SGAs is usually about 0.2–0.5 standard deviations, very large sample sizes would be needed in order to detect differences, and even larger sample sizes are required to rule them out. But the fact that there was even a trend for a superiority of amisulpride for cognition makes an undetected superiority of olanzapine highly unlikely. Based on the effect sizes

observed (0.4 for amisulpride, 0.2 for olanzapine, for the global cognitive index), one might rather anticipate that a study with high statistical power could demonstrate superiority of amisulpride.

Another issue is the number of dropouts. Of 52 subjects randomized, 15 dropped out of the study before week 4. The number of subjects lost to follow-up is not uncommon for such studies (Martin *et al*, 2002; Meyer-Lindenberg *et al*, 1997; Purdon *et al*, 2001; Volavka *et al*, 2002; Santarlasci and Messori, 2003) and there was no indication of selective attrition in one group, which might have biased the results.

The follow-up interval for the study has been 8 weeks, with several patients dropping out of the study after 4 weeks. Thus, stronger cognitive effects of one substance over the other one might have emerged after long-term treatment, but such a delay would have little pharmacological plausibility, and many previous studies have observed improvements within the first weeks of olanzapine treatment (Harvey *et al*, 2003).

In this study, the first neuropsychological assessment took place after subjects were already medicated for 0–8 days (mean $\pm$ SD 4.8 $\pm$ 2.2, median 5 days). We opted for this schedule in order to ensure sufficient attention and motivation to comply with the testing protocol. Subjects in both treatment groups did not differ from each other with regard to psychopathology or cognition at the first testing, and possible differences between groups therefore would not have been affected by this testing schedule. This procedure might underestimate the absolute benefit of either treatment, since some early cognitive improvements would go undetected. However, this shortcoming is irrelevant for the hypothesis under investigation.

The effect sizes of cognitive improvement in the present study are very similar to those summarized by Harvey and Keefe (2001) for studies of SGAs. Harvey and Keefe (2001, Table 4) reported effect sizes between 0.13 (for immediate memory) and 0.43 (for verbal fluency), for studies of 4–8 weeks duration where the amount of improvement was most often determined by switching patients from older antipsychotics to newer ones (the rather small change of declarative memory found in the present study is probably caused in part by a more difficult version of the auditory verbal learning test used at the third testing). Thus, the present trial achieved small to moderately sized cognitive improvements across 8 weeks (0.14–0.34 for the entire sample), equivalent to other studies with SGAs. It is therefore highly unlikely that the failure to find differential effects of olanzapine and amisulpride is the result of methodological limitations that would have precluded to identify such effects.

Amelioration of cognitive deficits was correlated with reduced negative but not with reduced positive symptoms across the duration of the trial. The independence of cognitive deficits from positive symptoms has been shown in previous studies (Breier *et al*, 1991; Green, 1996; Hughes *et al*, 2003). The improvement in negative symptoms and in cognitive deficits may partly be mediated by common underlying mechanisms, presumably dopaminergic, that are pharmacologically influenced by both atypical drugs studied here.

Olanzapine and amisulpride both exerted moderately sized positive effects on several aspects of cognition, and this is probably more than a trivial test repetition or training effect. It should be noted, though, that studies on cognitive effects of antipsychotics so far never assessed whether the treatment really narrows the gap between normal performance and the performance of patients, simply because a normal control group has not been studied with the same tests repeatedly. This issue requires further scrutiny. However, SGAs may allow for improvements to take place (due to practice or due to effects beyond practice), while FGAs may preclude such improvements at traditional dosage levels (eg by impairing cognitive and motor learning in the basal ganglia) or may even impede performance (by slowing motor functioning or by requiring anticholinergic medication to control EPMS) (CWGoCTE, 1998; Kasper and Resinger, 2003; Carpenter and Gold, 2002). Interestingly, low-dose haloperidol (5 mg average daily dose) was found to result in similar cognitive improvements in schizophrenic patients as risperidone (6 mg average daily dose) over 2 years (Green *et al*, 2002), implying that even FGAs may have neurocognitive benefits at lower than traditional doses.

Our data suggest that 5-HT_{2A} blockade is not the common denominator of SGAs beneficial effects on cognition. The same is true for their clinical efficacy with regard to negative and positive symptoms.

This study cannot be taken as evidence against a common mechanism behind SGAs, the identification of which would possibly facilitate future drug development. One alternative hypothesis focuses on faster dissociation of all SGAs from the D_2 receptor (Kapur and Seeman, 2001), and this would be a common mechanism for amisulpride and olanzapine (and other SGAs). Data reported in Seeman (2002) show that amisulpride dissociates as fast as clozapine from D_2 receptors. The comparable clinical effectiveness of amisulpride with serotonergic SGAs has been interpreted by Lewis (2002) as indirect evidence for the fast dissociation hypothesis of Kapur and Seeman (2001). By the same token, the present data on equal cognitive effectiveness would also constitute indirect evidence for this fast dissociation hypothesis. At any rate, they provide direct evidence against a crucial role of 5-HT_{2A} antagonism for obtaining cognitive effects in schizophrenia.

Serotonin receptors may still play a role for future drug developments. For example, 5-HT_{1A} agonism increases dopaminergic and cholinergic neurotransmission in the cortex, and may therefore be a mechanism to improve cognition (Ichikawa and Meltzer, 1999; Meltzer, 1999). In fact, a clinical pilot study by Sumiyoshi *et al* (2001) found that the selective 5-HT_{1A} agonist tandospirone, given as an add-on therapy, improved executive function and verbal memory in schizophrenic patients treated with conventional antipsychotics, while placebo did not. Similarly, 5-HT_{2A} blockade with mianserin as an add-on improved some aspects of memory (but not executive functions) in schizophrenics treated with FGAs (Poyurovsky *et al*, 2003).

These findings are theoretically important for a better understanding of neurobiological mechanisms underlying the efficacy of SGAs. While animal data are valuable to derive hypotheses for a better understanding of drug actions in patients, these hypotheses have to be tested clinically. Cognitive impairments in schizophrenia continue to pose a burden on patients and caregivers, despite the

modest improvements brought about by the SGAs. Only hypotheses confirmed by clinical data can guide the rational search for better drug treatments in the future.

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