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Treatment with amisulpride and olanzapine improve neuropsychological function in schizophrenia

Ann M. Mortimer[1]*, Eileen Joyce[2], Krishnapillai Balasubramaniam[3], Prasoon C. Choudhary[4] and Packeeruther T. Saleem[5] for the SOLIANOL Study Group

[1]*University of Hull, Hull, UK*
[2]*UCL Institute of Neurology, Queens Square, London, UK*
[3]*Calnwood Court, Luton, UK*
[4]*St Tydfil's Hospital, Mid Glamorgan, UK*
[5]*Queen's Park Hospital, Lancashire, UK*

Objectives Although antipsychotic drugs control acute psychotic manifestations of schizophrenia, improving cognitive symptoms is also important for long-term prognosis.
Methods Three hundred and seventy-seven adult patients with acute psychosis were randomised to either amisulpride (200–800 mg/d) or olanzapine (5–20 mg/d) for 6 months. Neuropsychological performance was assessed at inclusion and after 6 months in a subgroup of 26 subjects (11 treated with amisulpride and 15 with olanzapine) using the Auditory Verbal Learning Test (AVLT), the Trail Making Test (TMT) and the Controlled Oral Word Association Test (COWAT).
Results The improvement in BPRS score was similar in both treatment groups. No significant differences in test performance between groups were observed at inclusion. After 6 months, AVLT scores increased by 8.7 points in the amisulpride group and by 2.3 points in the olanzapine group ($p = 0.049$). Completion speed in the TMT increased by 17.4 s (amisulpride) and 15.4 s (olanzapine) for Part A and by 39.8 and 48.8 s, respectively for Part B. Performance in the COWAT improved little in both groups.
Conclusions Both amisulpride and olanzapine produce sustained improvement in certain measures of neuropsychological performance in patients with schizophrenia; a significant improvement in score on the AVLT was observed only with amisulpride.

KEY WORDS — amisulpride; olanzapine; schizophrenia; cognitive function; neuropsychological testing

INTRODUCTION

The majority of subjects with schizophrenia have markedly impaired cognitive function, and this is now considered to be a core feature of this condition (Addington *et al*., 1991; Saykin *et al*., 1991; McGurk *et al*., 2000; Flashman and Green, 2004; Lewis, 2004). Cognitive defects are apparent in the first episode of psychosis (Hoff *et al*., 1992; Mohamed *et al*., 1999), in treatment-naive subjects (Saykin *et al*., 1994) and may be found during the prodromal phase before overt signs and symptoms of schizophrenia are manifest (Davidson *et al*., 1999). Cognitive impairment is associated with poor functional outcome and long-term prognosis (Green, 1996; McGurk *et al*., 2000). As such, the presence of such defects is an important determinant of quality of life (Heslegrave *et al*., 1997) and of the medical and social cost of schizophrenia (Sevy and Davidson, 1995).

For these reasons, improvement in impaired cognitive function in schizophrenia has been identified as an important treatment goal in the overall management of this condition (Davidson and Keefe, 1995; Harvey *et al*., 2004). It has been generally considered that conventional antipsychotic drugs, in spite of providing effective treatment of psychosis, have little impact on cognitive symptoms and may even be deleterious due

* Correspondence to: A. M. Mortimer, Department of Psychiatry, The Hertford Building, The University of Hull, Cottingham Road, Hull HU6 7RX, UK. Tel.: +44 (0) 1482 464564. Fax: +44 (0) 1482 464569. E-mail: A.M.Mortimer@hull.ac.uk

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to sedative or anticholinergic side-effects (Cassens *et al*., 1990; Bilder *et al*., 1992; Mortimer, 1997), although more systematic analyses suggest that these drugs do have a modest benefit (Mishara and Goldberg, 2004). However, there is evidence that the newer atypical antipsychotic drugs may have a more incisive effect on cognitive symptoms (Keefe *et al*., 1999; Meltzer and McGurk, 1999; Harvey and Keefe, 2001). A meta-analysis of the overall effects of the newer atypical antipsychotic drugs has showed that they conferred a statistically significant greater improvement in performance in neuropsychological tests of cognitive function than the conventional drugs (Keefe *et al*., 1999). Nonetheless, the results obtained have not been entirely consistent and the real long-term benefit of such an effect on cognition remains to be demonstrated (Carpenter and Gold, 2002).

Several factors contribute to the variability in the results of published studies with atypical antipsychotic drugs. These include methodological differences related to the neuropsychological tests used, the dose of antipsychotic and the choice of patient, low sample sizes in many studies and the lack of randomisation (Carpenter and Gold, 2002; Harvey and Keefe, 2001). Most of the studies of atypical antipsychotic drugs on cognitive function have been performed in subjects with predominantly negative symptoms, as it is in these patients that cognitive dysfunction is the most prominent (Addington *et al*., 1991). In addition, it is important to take into account that atypical antipsychotics are not a homogeneous class of drug, differing in their pharmacological specificity, their side-effect profiles and their clinical profiles. For this reason, different drugs may affect neuropsychological performance in different ways. Indeed, a recent comparative study has demonstrated that atypical antipsychotics with a pronounced 5-HT_2 serotonin receptor antagonist activity differ in their impact on neuropsychological function to those atypical agents devoid of such a pharmacological effect (Tyson *et al*., 2004).

We have undertaken an analysis of changes in performance on a small battery of neuropsychological tests in a subgroup of subjects participating in a randomised, comparative trial of amisulpride and olanzapine presenting with acute psychotic manifestations of schizophrenia (Mortimer *et al*., 2004). This study demonstrated that both drugs provided comparable antipsychotic efficacy, and provided an opportunity to evaluate whether this antipsychotic effect is accompanied by a comparable amelioration of neuropsychological function.

These two antipsychotic drugs have quite different mechanisms of action, but both have been demonstrated in previous studies to improve neuropsychological performance. Amisulpride is an atypical antipsychotic that has a selective affinity for D2 and D3 dopamine receptors (Schoemaker *et al*., 1997), with efficacy in positive and primary negative schizophrenic syndromes (Leucht *et al*., 2002) and a low incidence of extrapyramidal effects (Leucht *et al*., 2002). Studies with amisulpride in healthy volunteers have provided evidence that this drug, unlike haloperidol, is devoid of deleterious effects on cognitive function in healthy volunteers (Peretti *et al*., 1997; Legangneux *et al*., 2000). More recently, three studies have demonstrated that amisulpride can improve aspects of neuropsychological performance in patients with schizophrenia (Tyson *et al*., 2004; Vaiva *et al*., 2002; Wagner *et al*., 2005). Olanzapine is a relatively unselective atypical antipsychotic with high affinity for 5-HT2 serotonin receptors as well as dopamine D2 receptors (Bymaster *et al*., 1997), a low incidence of extrapyramidal effects (Leucht *et al*., 1999), efficacy in acute psychosis (Leucht *et al*., 2002) and possible activity on affective symptoms (Collaborative Working Group on clinical trial evaluations, 1998). Improvement in neuropsychological performance has been observed in several studies with this antipsychotic (Purdon *et al*., 2000; Cuesta *et al*., 2001; Bilder *et al*., 2002; Sharma *et al*., 2003; Harvey *et al*., 2003; Stip *et al*., 2003; Keefe *et al*., 2006). A recent meta-analysis has evaluated neuropsychological change in 41 clinical trials of patients with schizophrenia treated with atypical antipsychotics, including 13 trials involving olanzapine (Woodward *et al*., 2005). The meta-analysis identified robust improvements in the global cognitive index and in seven out of nine domains of neuropsychological performance in olanzapine-treated patients. This meta-analysis did not include any studies with amisulpride.

A previous randomised trial compared the effects of acute treatment (2 months) with amisulpride or olanzapine on cognitive functions and found beneficial effects with both drugs on several neuropsychological domains (Wagner *et al*., 2005). This report describes changes in performance on neuropsychological tests of cognitive function in subjects with acute psychotic manifestations of schizophrenia treated for 6 months with amisulpride or olanzapine.

METHODS

This study was performed in a subset of subjects participating in a large multinational randomised

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clinical trial (SOLIANOL) comparing the effect of treatment with amisulpride and olanzapine in acute psychosis. All patients included in any one of the eight participating centres in the United Kingdom were eligible for the substudy. Full details of the methodology of the principal study have been published previously (Martin *et al*., 2002; Mortimer *et al*., 2004).

Subjects

The subjects were required to be aged between 18 and 65 years with a diagnosis of schizophrenia (paranoid, disorganised or undifferentiated type) or of schizophreniform disorder according to the DSM IV criteria (American Psychiatric Association, 1994). Inclusion criteria included a score on the Brief Psychiatric Rating Scale (Overall and Gorham, 1962) of at least 36 and a score on the positive symptoms subscale of the Positive and Negative Syndrome Scale (Kay *et al*., 1987) higher than the score on the negative symptoms subscale. Exclusion criteria extended to pregnant and lactating women, and those women of childbearing age not using an adequate means of contraception, and contra-indications to amisulpride or olanzapine as defined in the Summary of Product Characteristics for the two drugs. In addition to these entry criteria for the principal SOLIANOL study, subjects were required to have an IQ over 80 using the National Adult Reading Test (NART; Nelson, 1982) and to be able and willing to cooperate with the study procedures in order to participate in the neuropsychological study.

Treatment and study procedures

A thorough clinical and psychiatric examination was carried out at a screening visit when a single-blind placebo washout period of 3–6 d was initiated. At the baseline visit, inclusion and exclusion criteria were reassessed and eligible patients were randomised to one of the two treatment arms, either amisulpride 400 mg/d or olanzapine 10 mg/d. After 1 week of treatment, the medication doses were allowed to be adjusted between 200 and 800 mg/d for amisulpride and to 5–20 mg/d for olanzapine, according to individual patient response and tolerability. The double-blind treatment period continued for 6 months from the baseline visit.

Outcome assessments

Psychiatric outcome was assessed by measurements of PANSS scores at baseline, 2 and 6 months, from which BPRS scores were reconstituted *a posteriori*. The change in BPRS score from baseline to 6 months was the primary efficacy outcome measure for the study. Extrapyramidal symptoms were assessed using the Abnormal Involuntary Movements Scale (AIMS; National Institute of Mental Health, 1976) and by adverse event reporting.

Three measures of neuropsychological function were made at the baseline visit and at the 6 week and 6 month follow-up visits. Learning and memory were assessed by the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964), total score over the first five trials were determined. Processing speed and cognitive flexibility were assessed using the Trail Making Test (TMT; Reitan, 1958). Verbal fluency was measured by the Controlled Oral Word Association Test (COWAT; Bechtoldt *et al*., 1962). These tests were chosen because the functions that they evaluate are known to be significantly compromised in patients with schizophrenia, even in the presence of intact general cognitive function (Clare *et al*., 1993). No other neuropsychological test was administered.

Data on safety were also collected and were published with the results of the SOLIANOL study (Mortimer *et al*., 2004).

Statistical analysis

The Intent-To-Treat (ITT) population was defined as all patients randomised and exposed to treatment for at least 14 d and providing at least one post-baseline neuropsychological assessment, either at 6 weeks or 6 months, or at the time of premature study discontinuation if this occurred between the 6 weeks and 6 months study visit. Missing data, except for baseline, were replaced with the last available valid post-baseline observation, according to the principle of Last Observation Carried Forward (LOCF). A descriptive analysis of the observed case (OC) population, restricted to those patients who provided neuropsychological data at 6 months, was also performed.

Difference in scores between baseline and study end were compared between treatment groups (olanzapine, amisulpride) using analysis of covariance taking baseline values as a covariate. Rank values were used for this analysis. Within group comparisons were performed with the non-parametric paired Wilcoxon test. A probability level of <0.05 was taken to be statistically significant.

Ethics

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment), Good Clinical

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Practices (European Guidelines) and pertinent European and United Kingdom legal and regulatory requirements. Written informed consent was obtained from each subject. Patients were free to withdraw from the study at any time for any reason, without effect on their medical care. The protocol was submitted to and approved by the South-East Multicentre Research Ethics Committee.

RESULTS

Subjects included

A total of 377 patients with predominant positive symptomatology were randomised to treatment with either amisulpride or olanzapine in the SOLIANOL study (Mortimer *et al*., 2004). Of these, 36 subjects were enrolled in the participating British centres. Thirty-two of these had a verbal IQ (NART) score of over 80 (amisulpride group, mean score $\pm$ SD = 105.25 $\pm$ 11.7; olanzapine group, mean score $\pm$ SD = 108.21 $\pm$ 8.9, with no significant difference observed between the two groups) and were thus eligible for the neuropsychological study. Six of these patients, however, refused to participate. A baseline neuropsychological assessment was performed in the remaining 26 subjects. In total, 23 subjects provided neuropsychological data at baseline and at least one other time point and formed the ITT population. Eleven of these subjects received amisulpride (seven men and four women) and 15 subjects received olanzapine (11 men and four women). Of the three other subjects, two in the amisulpride group discontinued the study prematurely, one due to an intercurrent illness and one who was uncooperative, and one in the olanzapine group who declined to participate further. Eight and ten patients, respectively, were assessed both at baseline and at study end, and were the subject of the OC analysis. One amisulpride-treated patient did not complete the study due to discontinuation for an adverse event after 10 weeks. Four patients in the olanzapine group failed to complete the study, three premature study discontinuations, one for an adverse event at 19 weeks, one for lack of efficacy at 10 weeks and one for another reason at 24 weeks, and one patient who no longer wished to pursue the neuropsychological testing. A patient flow diagram is presented in Figure 1.

For comparison, the sex ratio in the overall SOLIANOL population was 64.9% male. The mean age $\pm$ SD of the subjects in the amisulpride subgroup was 44 $\pm$ 12.6 years (range 22–63 years) and 38.07 $\pm$ 10.4 years (range 21–54 years) in the olanzapine subgroup. These figures compare with a mean age in the overall SOLIANOL population of 38.2 years for the amisulpride group and 37.4 years for the olanzapine group.

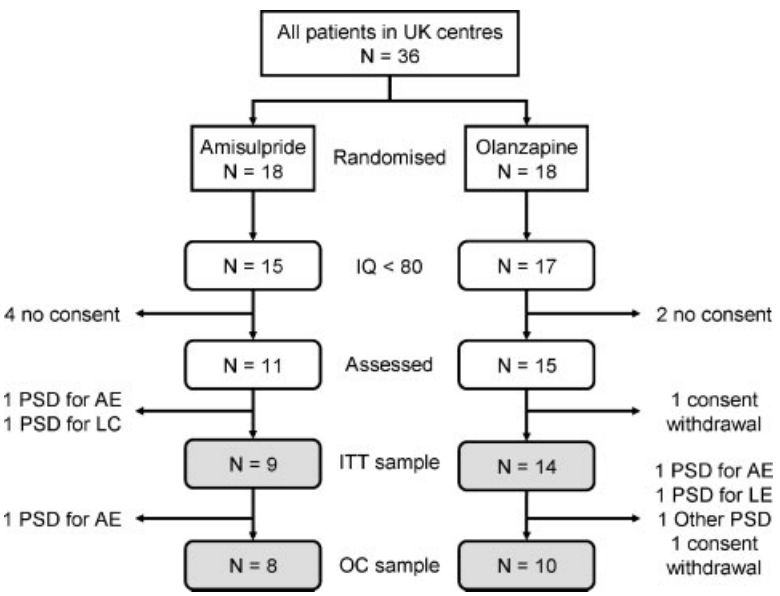

Figure 1. Patient flow diagram. AE, adverse event; IQ, intelligence coefficient; ITT, Intent-To-Treat; LC, lack of cooperation: LE, lack of efficacy; OC, observed case; PSD, premature study discontinuation

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Table 1. Evolution of BPRS score over the study period

	Neuropsychological study		Total SOLIANOL population	
	Amisulpride ($N = 11$)	Olanzapine ($N = 16$)	Amisulpride ($N = 189$)	Olanzapine ($N = 188$)
Baseline	30.8 [7.8]	35.3 [10.7]	56.0 [9.8]	55.1 [9.7]
Month 2	14.4 [10.3]	17.5 [9.3]	38.4 [12.7]	38.7 [13.7]
Change from baseline	16.5 [9.0]	17.8 [10.3]	17.6 [13.9]	16.3 [13.4]
Month 6	10.6 [7.5]	13.9 [10.2]	37.7 [15.0]	36.8 [14.5]
Change from baseline	20.2 [10.3]	21.4 [13.6]	18.3 [16.2]	18.2 [15.3]

Data are presented as mean [SD] values.

Psychiatric outcome

The BPRS scores at baseline were 30.8 in the amisulpride-treated subjects and 35.3 in the olanzapine-treated subjects (Table 1). These values are significantly lower than those observed in the SOLIANOL population as a whole. Over the course of the study, BPRS scores declined in both groups, with no significant difference in change from baseline between the two treatment groups. The extent of change from baseline in BPRS scores was closely comparable to that observed in the overall SOLIANOL population (Table 1).

Extrapyramidal effects

Extrapyramidal symptoms were not reported in any patient during the study. Scores on the AIMS decreased or remained stable in all patients except one in the olanzapine group, in which the score increased from one at baseline to seven after 6 months of treatment. No patient required antiparkinsonian medication during the study.

Prior and concomitant psychotropic medication

Medications taken in the month preceding inclusion and during the study that could possibly interfere with neuropsychological performance were assessed (Table 2). All patients except two in the amisulpride group and three in the olanzapine group were treated with an antipsychotic during the previous month. Two patients in the amisulpride group and three in the olanzapine group received an atypical antipsychotic. Depot antipsychotic medication, principally α-flupenthixol decanoate, was used by three patients in the amisulpride group and four in the olanzapine group. In addition, two patients in the amisulpride group were treated with a benzodiazepine during the previous month and two with an antidepressant. In the olanzapine group, six patients had received a benzodiazepine and four an antidepressant. Anticholinergic medication for the control of parkinsonian symptoms was used by four patients in the amisulpride group and two in the olanzapine group in the month prior to inclusion.

During the treatment period, three patients in each group received a benzodiazepine and one in the amisulpride group received an antidepressant (fluoxetine). Anticholinergic medication was not used during the study period.

Neuropsychological outcome

The total score in the RAVLT was similar in both study arms at baseline (Table 3). There was a significant difference in the baseline-adjusted mean change in score from baseline between the two treatment groups in favour of amisulpride (ANCOVA; F value $= 4.38$, $p = 0.049$). The absolute change from baseline was only significant in the amisulpride group ($p = 0.004$; Wilcoxon test; Figure 2) In the OC analysis, RAVLT scores increased from 31.5 ± 7.5 to 42.0 ± 6.4 in the amisulpride arm and from 31.5 ± 11.0 to 33.3 ± 11.3 on the olanzapine arm.

On both versions of the TMT, baseline scores were comparable between the two groups (Table 3). Completion times were significantly lower at study end compared to baseline in the amisulpride group for Part A (Wilcoxon test; $p = 0.023$) and in the olanzapine group for Part B (Wilcoxon test; $p = 0.019$). There was no significant difference in the adjusted mean change in score from baseline between the two treatment groups for either version of the TMT (ANCOVA; TMT A: F value $= 0.22$, $p = 0.648$; TMT B: F value $= 0.31$, $p = 0.584$; Figure 3). In the OC population, completion times for version A decreased from 71.3 ± 38.2 to 49.6 ± 32.3 s in the amisulpride group and from 65.3 ± 34.3 to 58.5 ± 36.4 s in the olanzapine group; and from 156 ± 149 to 122 ± 64 s in the amisulpride group and from 180 ± 122 to 155 ± 101 s in the olanzapine group for version B.

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Table 2. Prior and concomitant psychotropic medication

	In 4 weeks preceding inclusion				During study		
	AP	BDZ	AD	AC	BDZ	AD	AC
Amisulpride group ($N = 11$)							
1	Haloperidol	—	Citalopram	Procyclidine	—	—	—
2	Chlorpromazine + Trifluoperazine	—	—	—	—	—	—
3	—	—	—	Procyclidine	—	—	—
4	Trifluoperazine	—	—	Procyclidine	—	—	—
5	Pimozide	—	—	—	—	—	—
6	α-Flupenthixol*	—	—	—	—	—	—
7	Risperidone	—	—	—	—	—	—
8	α-Flupenthixol*	—	Fluoxetine	Procyclidine	—	Fluoxetine	—
9	α-Flupenthixol*	—	—	—	Diazepam	—	—
10	—	Nitrazepam	—	—	Nitrazepam	—	—
11	Quetiapine	Lorazepam + Zopiclone	—	—	Lorazepam + Zopiclone	—	—
Olanzapine group ($N = 15$)							
1	Zuclopenthixol*	—	Lofepramine	—	—	—	—
2	—	Oxazepam + Zopiclone	Amitriptyline	—	Oxazepam + Zopiclone	—	—
3	—	—	—	—	—	—	—
4	α-Flupenthixol*	Diazepam	—	Trihexyphenidyl	—	—	—
5	Quetiapine	—	Venlafaxine	—	Zolpidem	—	—
6	α-Flupenthixol*	—	—	Procyclidine	—	—	—
7	Chlorpromazine + Trifluoperazine	—	—	—	—	—	—
8	α-Flupenthixol*	Lorazepam	—	—	—	—	—
9	Haloperidol	Lorazepam	Paroxetine	—	—	—	—
10	—	—	—	—	—	—	—
11	Zuclopenthixol*	Lorazepam	—	—	Lorazepam	—	—
12	Haloperidol	—	—	—	—	—	—
13	Amisulpride	—	—	—	—	—	—
14	Fluphenazine*	—	—	—	—	—	—
15	Risperidone	Diazepam	—	—	—	—	—

AC, anticholinergic; AD, antidepressant; AP, antipsychotic (*depot form); BDZ, benzodiazepine or related.

On the COWAT, baseline scores were similar in the amisulpride and olanzapine treatment groups (Table 4). No significant changes in the number of acceptable words were observed over the study period in either treatment group on any of the three test modalities in either the ITT or the OC populations (Table 4).

DISCUSSION

This study demonstrated that treatment with amisulpride or olanzapine over a six-month period improves performance on two neuropsychological tests of cognitive function in subjects with acute psychotic episodes of schizophrenia. In RAVLT, a significant improvement was only observed for the amisulpride group, with a significant inter-group difference in favour of this drug. In the TMT, no inter-group differences were observed, and significant improvements were noted for the amisulpride-treated subjects for Part A and for the olanzapine-treated subjects for Part B. No improvements in performance were observed in the COWAT. Since baseline values are important determinants of subsequent performance in

Table 3. Baseline scores on the Rey Auditory Verbal learning Test (RAVLT) and the TMTs A and B

	Amisulpride	Olanzapine
RAVLT total score[a] range	32.4 [7.3] ($n = 9$) [22–43]	30.9 [11.2] ($n = 14$) [14–51]
TMT A (s)	77.3 [39.9] ($n = 9$)	65.9 [35.5] ($n = 14$)
TMT B (s)	195 [142] ($n = 8$)	183 [126] ($n = 14$)

Data are presented as mean [SD] values.
[a]Maximal score possible: 75.

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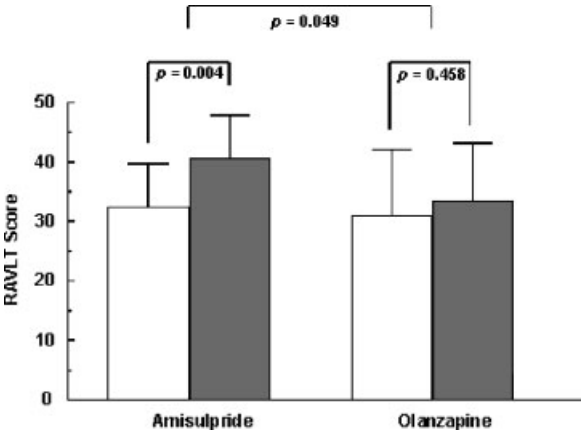

Figure 2. Rey auditory verbal learning test: Scores at baseline (open columns) and 6 months (filled columns) for subjects taking amisulpride or olanzapine

neuropsychological tests, the analysis of variance of treatment effects were adjusted for baseline values to ensure that the observed changes were really related to the treatment intervention.

On RAVLT, a test of learning and memory function, baseline scores were low. A significant improvement in score was observed with amisulpride but not with olanzapine. Using a visual recognition memory task, Tyson *et al*. (2004) have also reported that learning and memory performance in subjects with schizophrenia is improved by amisulpride but not by olanzapine or other agents with potent 5-HT_2 serotonin receptor antagonist activity. The apparent lack of effect of olanzapine on this outcome measure is, however, in disagreement with the results of a larger open-label Canadian study, showing increased scores in this test after 2 month's treatment with olanzapine (Stip *et al*., 2003). The difference may be attributable to the low sample size in our study, which could hide more modest treatment effects.

The TMT assesses attention and vigilance in Part A and strategy retention and management in Part B. Although the finding that the subjects treated with amisulpride perform better on Part A whereas those receiving olanzapine do better on Part B may suggest that the two drugs have an impact on different aspects of cognitive function, such interpretations should be treated with great caution given the small sample size and inter-subject variability. Indeed, previous studies have shown significant improvements on both parts of the TMT with amisulpride (Vaiva *et al*., 2002) and olanzapine (Harvey *et al*., 2003; Stip *et al*., 2003). On the other hand, Cuesta *et al*. (2001) reported a selective effect of olanzapine on Part B of this test, consistent with the present results.

On COWAT, baseline scores were very low compared to general population norms. A surprising finding of this study is that performance on this test was not altered by antipsychotic treatment, since improved verbal fluency has been one of the most robust findings with respect to the cognitive effects of atypical antipsychotic drugs (Keefe *et al*., 1999).

In comparison with the previous two-month comparative study of olanzapine and amisulpride (Wagner *et al*., 2005), similar treatment effects on TMT and absence of treatment effects on a verbal fluency task were observed. Unlike our own study, Wagner *et al*. used parallel versions of the test instruments in order to minimise bias from learning effects. Using analysis of variance with repeated

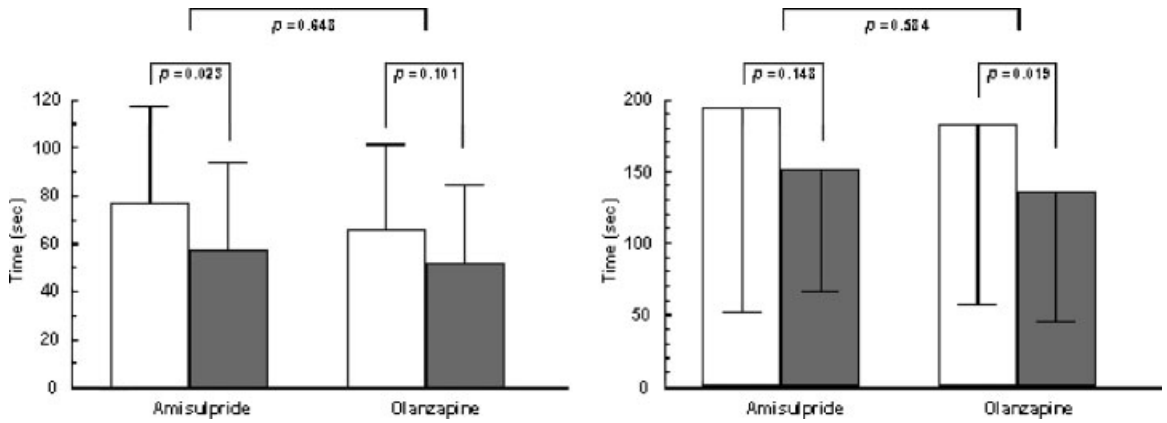

Figure 3. Trail Making Test (TMT): Completion times (s) at baseline (open columns) and 6 months (filled columns) for subjects taking amisulpride or olanzapine on Version A (left) and Version B (right)

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Table 4. Acceptable word scores on the controlled oral word association test

	ITT population		OC population	
	Amisulpride ($N=9$)	Olanzapine ($N=14$)	Amisulpride ($N=8$)	Olanzapine ($N=10$)
F+A+S				
Baseline	20.2 [7.8]	23.3 [11.7]	19.9 [7.4]	23.5 [11.3]
Month 6	22.0 [10.5]	24.1 [8.2]	22.9 [10.8]	21.6 [7.3]
Mean change	1.8 [6.5]	0.8 [6.3]	ND	ND
Animals				
Baseline	10.8 [5.6]	12.1 [6.3]	10.9 [5.3]	11.9 [6.1]
Month 6	10.1 [3.5]	11.5 [3.9]	10.4 [3.6]	10.6 [3.8]
Mean change	−0.7 [3.6]	−0.6 [4.0]	ND	ND

Data are presented as mean [SD] values for scores at baseline, study end at 6 months and mean change from baseline over the study period. ND, not determined.

measures, they reported a broader range of neurocognitive domains improved in patients treated with amisulpride than in those treated with olanzapine as well as a trend towards superiority of amisulpride. In addition, Tyson *et al*. (2004) also concluded that 15 patients treated with antipsychotics with low affinity for 5-HT_{2A} receptors (including seven patients receiving amisulpride) performed better on certain neurocognitive tests than did 29 patients treated with drugs with high affinity for 5-HT_{2A} receptors (including nine receiving olanzapine). Our data are not inconsistent with such a difference.

However, the results of the aforementioned studies, notably the absence of effects of olanzapine on verbal fluency and delayed recall, should be balanced against the results of the meta-analysis of studies of the neuropsychological effects of olanzapine (Woodward *et al*., 2005) where significant treatment effects of olanzapine on these two dimensions were observed, notably on verbal learning, with an effect size (within-group change score divided by its standard deviation) of 0.61.

Large double-blinded comparative studies in untreated patients which are carefully controlled for potential learning effects and for the effects of concomitant psychotropic medication need to be performed in order to address the relative efficacy of different atypical antipsychotic drugs on neuropsychological function in a more definitive fashion.

It should be noted that, in our study, the majority of patients had been receiving classical antipsychotic drugs in the month prior to inclusion. The improvements in neuropsychological function observed cannot, therefore, be imputed definitely to positive effects of amisulpride and olanzapine on neuropsychological outcome, but may represent simply the disappearance of the well-characterised negative cognitive impact of previous antipsychotic treatments following discontinuation of these drugs. In addition, practice effects are well documented for the neuropsychological tests used (Lezak *et al*., 2004). The study did not control for these by the use of parallel versions of the tests and practice effects may thus make a significant, if unknown, contribution to the improvements observed.

The principal limitation of this study was the low sample size, which limited the power of the study to detect relevant changes in performance. This limitation is shared, however, with many previous studies of the effects of antipsychotic drugs on cognitive function. An exception is the large comparative randomised trial of 377 subjects treated with risperidone or olanzapine reported by Harvey *et al*. (2003), which demonstrated significant improvement on a battery of tests after 2 months of treatment, but no difference in outcome between the two treatment arms. Second, the included patients were less psychotic at inclusion than the overall SOLIANOL study population, thus introducing a potential bias into the representativity of the findings. This is likely to be related to the inclusion criteria, with more ill patients being less likely to be willing or able to co-operate with neuropsychological testing. Third, benzodiazepine use was permitted during the study, which may be a confounding factor in determining neuropsychological performance, particularly in those patients taking long-acting drugs such as diazepam or nitrazepam. Nonetheless, the number of patients who actually received benzodiazepines was in fact quite low. Fourth, it should be recognised that the neuropsychological test battery used was not large enough to evaluate all domains of cognition which are

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usually affected in patients with schizophrenia. Finally, there are no data on whether the observed improvements in neuropsychological function were associated with amelioration of personal functioning, sufficient to raise quality of life or to reduce resource uptake. Therefore, the practical value of the neuropsychological effects demonstrated by these two antipsychotic drugs remains unknown.

In conclusion, this study provides further evidence that amisulpride and olanzapine can improve neuropsychological function in patients with acute psychotic manifestations of schizophrenia, and suggests that the two drugs may affect different aspects of performance.

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