HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2010; **25**: 116–125.
Published online in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/hup.1101

Neurocognition and its influencing factors in the treatment of schizophrenia—effects of aripiprazole, olanzapine, quetiapine and risperidone

M. Riedel, R. Schennach-Wolff*, R. Musil, S. Dehning, A. Cerovecki, M. Opgen-Rhein, J. Matz, F. Seemüller, M. Obermeier, R. R. Engel, N. Müller, H.-J. Möller and I. Spellmann

Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, Munich, Germany

Background To examine influencing variables of neurocognition in patients with schizophrenia and to predict cognition during antipsychotic treatment.
Methods Data were obtained from patients with an acute episode of schizophrenia participating in two double-blind and one open label trial comparing the effects of different atypical antipsychotics on cognition. In total, 129 patients were enrolled in this analysis. Cognitive function was assessed at admission, week 4 and 8. Efficacy and tolerability were assessed weekly using the Positive and Negative Syndrome Scale (PANSS) and the Simpson Angus Sale (SAS). Patients were treated with aripirazole, olanzapine, quetiapine and risperidone. Regression analysis including mixed effect models was performed.
Results A significant improvement in all cognitive domains was observed from baseline to week 8. Regarding the antipsychotic treatment applied quetiapine seemed to achieve the most favourable cognitive improvement. Negative and depressive symptoms, the patient's age and the concomitant and antipsychotic treatment applied were observed to significantly influence and predict neurocognition.
Conclusion The results may indicate that schizophrenia is a static disorder with trait and state dependent cognitive components especially in the memory domains. The influence of negative and depressive symptoms should be considered in daily clinical routine. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — schizophrenia; neurocognitive deficits; influencing variables; atypical antipsychotics

INTRODUCTION

The neurocognitive performance of patients with schizophrenia was found to closely correlate with several key outcome domains and mark a limiting factor for treatment success and rehabilitation (Kirkpatrick *et al*., 2006). Neurocognitive subdomains including executive functions, memory and attention differentially and independently influence the long-term course and outcome of schizophrenia (Green, 1996). Therefore, understanding influencing variables of neurocognition and thereby establishing methods to improve neurocognitive deficits are of special interest (Akdede *et al*., 2006).

In terms of clinical characteristics and their potential influence on cognition it is still unclear whether the course of cognition depends on baseline or course of disease variables. Some studies suggest that variables like age, duration of illness as well as dyskinesia might influence cognitive functioning (Heaton *et al*., 2001), others, however, do not (Klingberg *et al*., 2008). Similar inconsistencies in present data exist regarding an association between psychopathology and its influence on cognitive functioning. On the one hand authors found treatment-related modulation of neurocognitive deficits and psychopathologic symptoms to progress with significant independence (Lindenmayer *et al*., 2007), which could not be confirmed by others (Bilder *et al*., 2002).

Another controversial mediator variable is the antipsychotic treatment applied. Especially since atypical antipsychotics are available, there is an increasing amount of studies assessing the influence of antipsychotic medication on cognitive performance (Wittorf *et al*., 2008) with several studies stating advantages of the new compounds in the treatment of cognitive dysfunctions

* Correspondence to: R. Schennach-Wolff, Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, Nussbaumstreet 7 80336 Munich, Germany. Tel: 0049 0 89 5160 5511; Fax: 0049 0 89 5160 5857. E-mail: Rebecca.Schennach-Wolff@med.uni-muenchen.de

Received 5 May 2009
Accepted 20 January 2010

compared to typical compounds in double-blind controlled trails (Bilder *et al*., 2002; Harvey *et al*., 2003; Velligan *et al*., 2002). However, recent large clinical trials indicated only modest cognitive benefits of second-generation relative to first-generation antipsychotics (Hill *et al*., 2010). In a study on first-episode schizophrenia patients Davidson *et al*. found a moderate improvement in the cognitive test performance with no difference between treatment with haloperidol and treatment with atypical antipsychotics (Davidson *et al*., 2009). A meta-analysis comparing cognitive changes with haloperidol and atypical compounds concluded that a broader range of cognitive improvements can be observed with atypical antipsychotics (Woodward *et al*., 2007).

Interestingly, only a limited number of studies have been published comparing cognitive effects of different atypical antipsychotics among each other. Keefe *et al*. analysed olanzapine, quetiapine and risperidone in a 52-week comparison and found all compounds to produce significant improvements in neurocognition without finding a significant difference between treatments (Keefe *et al*., 2007). Harvey *et al*. evaluated social competence, social cognition and neuropsychological functioning comparing quetiapine and risperidone and found no overall differences between treatments and their impact on the different domains (Harvey *et al*., 2006). In contrast, Voruganti *et al*. found quetiapine to have cognition enhancing properties when compared to olanzapine (Voruganti *et al*., 2007). Comparing cognitive changes in the treatment with clozapine, olanzapine, quetiapine and risperidone Woodward *et al*. stated that these compounds produce a mild remediation of cognitive deficits in schizophrenia with every drug having differential effects within certain cognitive domains (Woodward *et al*., 2005).

When comparing only parts of the present patient population we were able to demonstrate that quetiapine produces a significantly greater improvement in the cognitive domain of reaction quality/attention compared to olanzapine, but no significant differences between quetiapine and risperidone (Riedel *et al*., 2007a,b). Comparison trials including aripiprazole, to our knowledge, have not been performed so far.

Therefore, on the background of current inconsistencies regarding potential influencing factors of cognition including the atypical antipsychotic treatment applied and missing data on the effects of aripiprazole aims of the present analysis were to

(i) examine the course of cognition and its influencing factors including the treatment applied and
(ii) predict cognition at discharge.

METHODS

Study design

The present study comprises data of three different trials sharing the same study design. All three studies were performed at the Ludwig-Maximilians-University Munich and described in detail elsewhere (Riedel *et al*., 2007a,b). This analysis comprises one investigator-initiated, parallel-group, double blind, 12-week trial comparing the effects of quetiapine and risperidone; one investigator-initiated, parallel-group, double blind, 8-week trial comparing the effects of quetiapine and olanzapine and one investigator-initiated, open label 8-week trial rating the effects of aripiprazole. All three trials were performed in hospitalized patients with an acute episode of schizophrenia. Additionally, all trials were performed by the same study registrars using the same measuring instruments and inclusion and exclusion criteria were identical for all trials. To compare data of these three studies only data of week 1–8 were analysed. Patients receiving previous, non-depot antipsychotic treatment underwent a 2-days washout period before randomization to reach baseline dopamine receptor occupancy levels and reduce the possibility of illness deterioration.

Patients

Inpatients suffering from a DSM-IV diagnosis of schizophrenia and aged between 18 and 65 years were eligible for study participation. Inclusion criteria comprised a Clinical Global Impression scale score >4 and a PANSS total score >60 (Positive and Negative Symptom Scale [PANSS]). Exclusion criteria included: substance abuse, dependence or intoxication, suicidal tendencies, significant medical history (head trauma, epilepsy, meningo-encephalitis), ECG or EEG abnormalities; laboratory testing (blood and urine) $>20\%$ different from reference ranges, pregnancy or lactation and treatment with clozapine within 4 weeks of enrolment. All patients had to give written informed consent according to procedures approved by the ethics committee of the medical faculty of the University of Munich prior to study inclusion.

Treatment

A fixed-dose initiation schedule was used during the first week of treatment. Quetiapine was initiated as follows: 50 mg on Day 1, 100 mg on Day 2, and then daily 100 mg increments until reaching 600 mg/day. Risperidone was initiated at 2 mg/day on days 1 and 2, increasing to 4 mg/day on Days 3–5 and 6 mg/day on

DOI: 10.1002/hup

days 6 and 7. Olanzapine was initiated as follows: 10 mg at Day 1, titration up to 15 mg/day within the first 6 days. Thereafter, study medication was flexibly dosed according to clinician's judgment between 400 and 800 mg/day quetiapine, 4–8 mg/day risperidone, 10–20 mg/day olanzapine. Aripiprazole was also flexibly dosed according to clinician's judgment ranging from 5 to 30 mg/day.

In the event that a study participant did not respond effectively to the maximum dose, the patient was withdrawn from the study. Anticholinergic medication (biperiden hydrochloride $\leq$8 mg/day) was administered to treat EPS. Concomitant lorazepam ($<$4 mg) and zopiclone ($<$22.5 mg) were allowed to counteract agitation and sleep problems.

Neurocognitive test battery

The neurocognitive test battery was administered at baseline and following 4 and 8 weeks of treatment. The neurocognitive tests were chosen to represent a range of reliable and validated tests, which have already been used in similar trials. The used tests were grouped into six cognitive domains:

Working memory: To assess the working memory function, auditory working memory and visual working memory the Rey Auditory Verbal Learning Test (RAVLT) (lists 1 and 2, trial 1) (Schmidt, 1996) the letter-number span sequencing task (Gold *et al*., 1997) and the self-ordered-pointing task (SOPT) (Gutbrod *et al*., 1989) were used.

Verbal memory: The RAVLT (list 1, trials 1–5, 6–8) was applied to analyse the verbal declarative memory function.

Reaction time: The Neurobat S-Short Version (Wiebel *et al*., 1995) and the Trials A test (Reitan, 1958) was used to evaluate visuomotor speed.

Reaction quality/attention: The Neurobat S—short version (Wiebel *et al*., 1995) with the Duration of attention trial was performed to examine attention and sensomotor flexibility.

Executive function: To assess the general psychomotor function and measure category and letter fluency the Trails B test and the verbal fluency and category fluency (Spreen and Benton, 1965) were applied.

Visual memory: The memory of non-verbal stimuli and the visuospatial working memory were examined using the Wechsler memory scale-revised (Hawkins, 1999) and the one point test (Keefe *et al*., 1995).

Premorbid intelligence was ascertained using the multiple choice word Test-B (MWT-B) during the initial assessment. The vocabulary test results correlate with 'crystallised intelligence', which is supposed to remain stable during adulthood and is relatively independent of concurrent psychopathology. The test battery took between 90 and 120 min to complete. Three different parallel versions of the neurocognitive tests at the three test sessions were used to limit practice effects, except of the Neurobat-S—short version, the one-point test and SOPT. In line with LoSasso *et al*. alternate forms of the Trails A and B were used (LoSasso *et al*., 1998) and the LNS by Gold was applied (Gold *et al*., 1997). Regarding the WMS-R different elements were used at follow-up which has been performed by several other authors (Schuurman *et al*., 2002). A global cognitive index was constructed by adding and averaging the *z*-scores from the individual cognitive domains.

Clinical assessments

Clinical researchers assessed DSM-IV diagnosis on the basis of the German version of the Structured Clinical Interview for DSM-IV (American Psychiatric Association, 1994). During interviews with patients, relatives and care providers sociodemographic variables (partnership, employment state) and course-related variables such as age at onset, duration of untreated psychosis or episodes of illness were collected using a standardized documentation system (BADO) (Cording, 1998).

Symptom severity was assessed via the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay *et al*., 1988). Illness severity was measured using the Clinical Global Impression Improvement Scale (CGI-I) (Guy, 1976). To quantify antipsychotic side effects the Simpson-Angus Scale (SAS) was used. Adverse effects were recorded as additional indicators of tolerability throughout the trial.

Ratings were performed within the first 3 days after admission and weekly during hospital stay until discharge. All raters had been trained using the applied scales. A high inter-rater reliability was achieved (ANOVA-ICC $>$ 0.8).

Statistical analysis

In order to describe and analyse the results of the cognitive tests performed *z*-scores for each cognitive domain were calculated by using data from a normative sample. The improvement of the cognitive domains was analysed separately for each applied antipsychotic. For the comparison of two samples the *t*-test was used. The Kruskal–Wallis test was applied as non-parametric method of testing the hypothesis that several populations have the same continuous distribution. To

DOI: 10.1002/hup

analyse differences between the applied antipsychotics the null hypothesis was tested using ANOVA.

To examine the two study aims two different statistical models were applied: (1) mixed model regression analysis to examine influencing variables and (2) regression analysis without random effects to predict cognition at discharge.

In order to identify influencing variables of the patients' cognition during the study, baseline (e.g. psychopathology) and course-related variables (e.g. time point of treatment) were included in the mixed model. However, the prediction model only considered baseline variables since the aim was to predict cognition at discharge at the earliest possible time point. The estimates for the nominal data of the prediction model were described in dummy coding (Fahrmeir *et al*., 2007). In dummy coding for each nominal variable one reference level is chosen to which the estimates of the other levels refer.

(1) *Mixed models*: A random patient effect with intercept and slope was modelled. Using backward selection on the basis of LQ-tests the final model was found due to all possible fixed effects.

(2) *Regression analysis*: Using backward selection on the basis of AIC-values the final model was found due to all possible influencing variables.

For quantifying the goodness of fit a 10-fold cross validation with quadratic loss function was used to calculate the root means square error. Data analyses were carried out using the program R 2.8.1. (21).

RESULTS

Patients and treatment

In total, 129 patients with DSM-IV schizophrenia completed cognitive function tests at baseline, week 4 and 8. Of these, 83 were male and 46 female. The mean age was 33.54 (±11.29) years. No significant differences were found between the different treatment groups regarding sociodemographic variables such as age at onset, or duration of illness.

Fifty-two patients were treated with aripiprazole, 23 with olanzapine, 17 with risperidone and 37 with quetiapine. The mean dosage of 8 weeks of treatment was 12.48 (±3.4) mg/day for aripiprazole, 580 (±170.2) mg for quetiapine, 16 (±5.4) mg for olanzapine and 5 (±2.3) mg for risperidone. 73 patients had received antipsychotic pre-treatment, 56 patients were drug-naive. Of the pre-treated patients 58 patients (79%) had received atypical antipsychotics, 12 patients (16%) typical antipsychotics and 4 patients (5%) depot antipsychotics before hospitalisation. Anticholinergic medication (biperidene hydrochloride ≤6 mg/day) was administered in 27 patients (21%) after EPS were present. Concomitant lorazepam (≤2 mg/day) and diazepam (≤10 mg/day) were prescribed for 79 patients (61%) to counteract agitation. Insomnia was medicated using zopiclone (≤15 mg/day) in 64 patients (50%). Benzodiazepines, biperidene and zopiclone had to be discontinued at least 24 h prior to neurocognitive testing to assure an unaffected result. Propanolol (≤60 mg/day) was administered when akathisia occurred in eight patients (14%).

Cognition

A significant improvement in all cognitive domains was observed from baseline to week 8. (Table 1). The mean global cognition index *z*-scores from baseline to week 8 are shown in Figure 1. In Table 2 results of the neuropsychological tests comparing the different antipsychotic treatments applied are shown. Figure 2 shows the mean global cognition index *z*-scores from baseline to week 8 comparing aripiprazole, olanzapine, quetiapine and risperidone indicating the greatest cognitive improvement for the quetiapine treated patient subgroup.

Comparing patients with antipsychotic pre-treatment and drug naive patients no significant difference was found regarding cognitive improvement ($p = 0.781$). Furthermore, no significant association was found between cognitive performance and antipsychotic dosage ($p = 0.241$).

Table 1. Median and range of the improvement of cognitive domains from baseline, weeks 4 and 8. The *p*-value refers to the improvement from baseline to week 8

	Baseline	Week 4	Week 8	*p*-value
Working memory	−0.077 (4.73)	0.095 (3.977)	0.186 (4.4045)	<0.001
Reaction time	−0.101 (9.003)	0.098 (4.119)	0.09 (4.4226)	0.014
Reaction quality	0.052 (4.92)	0.208 (5.33)	0.22 (3.137)	<0.001
Verbal memory	−0.243 (4.333)	−0.033 (4.017)	0.112 (5.665)	<0.001
Executive function	−0.039 (2.217)	0.055 (2.922)	0.104 (2.537)	0.019
Visual memory	0.092 (4.157)	0.106 (±3.345)	0.172 (3.324)	<0.001
Cognition index	−0.101 (2.849)	0.006 (±2.482)	0.093 (2.601)	<0.001

DOI: 10.1002/hup

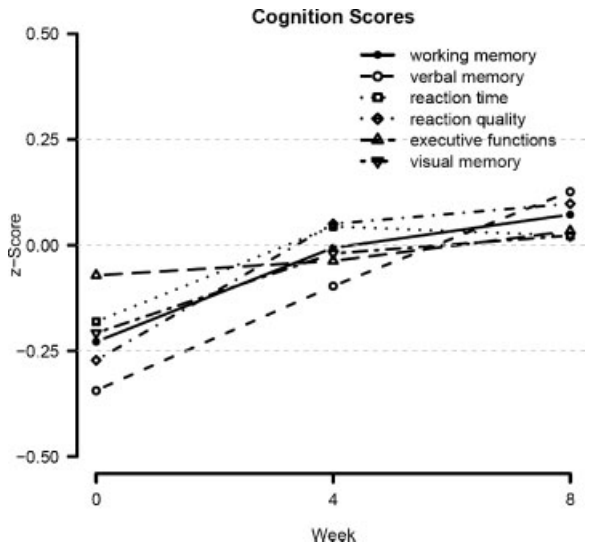

Figure 1. Mean global cognition index *z*-scores of different cognitive domains from baseline to week 8

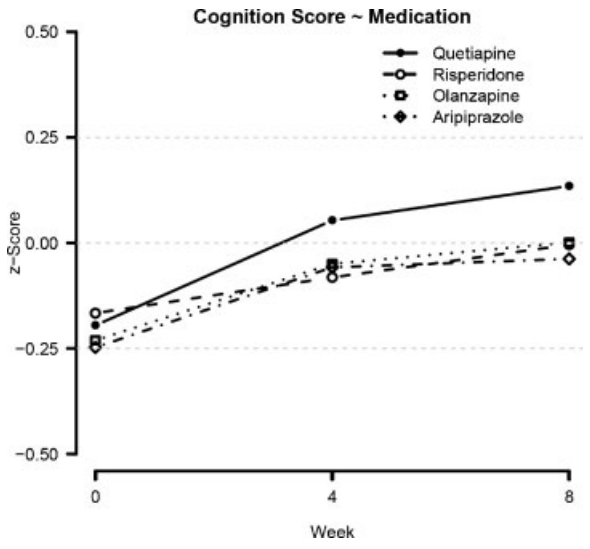

Figure 2. Cognition scores of all cognitive domains comparing the antipsychotic treatment applied from baseline to week 8

ANOVA-analysis revealed no significant difference between the mean *z*-scores of the different antipsychotics applied ($p = 0.16$).

Efficacy and tolerability

All PANSS subscores and PANSS total score improved significantly from baseline to week 8 ($p = 0.0000$). Applying the Kruskal–Wallis test no significant differences between medication groups regarding PANSS total score improvements were found ($p = 0.06$). The incidence of extrapyramidal side effects increased from baseline to week 8 ($p = 0.0605$).

Mixed model regression analysis

Applying mixed models potential influencing variables of cognition could be revealed for cognitive domains (Table 3). The patient's age was consistently associated with a favourable cognitive performance in terms that older patients showed greater impairments in their cognition. Other significant influencing variables were the PANSS negative and positive subscore as well as the application of lorazepam as concomitant medication.

Regression analysis

As age, PANSS negative and positive subscores were revealed to be significant predictors of several cognitive domains the significant influence of these variables could be confirmed (Table 4). The antipsychotic medication applied was only evaluated significant predictor for the cognitive domain working memory indicating that quetiapine showed the most positive influence on working memory.

DISCUSSION

Course of cognitive deficits and the influencing variable of the antipsychotic treatment applied

In the present study, we found a significant improvement in all cognitive domains from admission to week

Table 2. Improvement of cognitive domains of all patients from baseline to week 8 according to the antipsychotic treatment applied

	Quetiapine	Risperidone	Olanzapine	Aripiprazole
	$N = 37$	$N = 17$	$N = 23$	$N = 52$
Working memory	0.0000	0.2248	0.0001	0.134
Verbal memory	0.0000	0.2440	0.0470	0.131
Reaction time	0.4604	0.0388	0.7132	0.009
Reaction quality	0.0002	0.2742	0.5667	0.009
Executive function	0.1490	0.4701	0.8107	0.265
Visual memory	0.0205	0.1185	0.0054	0.213
Cognition index	0.0000	0.0313	0.0046	0.001

DOI: 10.1002/hup

Table 3. Mixed model regression analysis for the evaluation of influencing variables from admission to week 8 for each cognitive domain

	Value	Std. error	DF	*t*-value	*p*-value
Working memory					
PANSS negative subscore	−0.0096	0	201	−2.4	**0.017**
Age	−0.0271	0	121	−5.55	**<0.001**
Verbal memory					
Age	−0.0282	0.01	126	−4.15	**<0.001**
Reaction time					
PANSS negative subscore	−0.0188	0.01	110	−2.04	**0.044**
PANSS general psychopathology subscore	−0.0092	0.01	110	−1.16	0.248
Reaction quality/attention					
PANSS general psychopathology subscore	−0.0215	0.01	115	−2.84	**0.005**
Age	−0.0292	0.01	67	−4.01	**<0.001**
Executive functioning					
Age	−0.0125	0	123	−4.08	**<0.001**
Visual memory					
PANSS general psychopathology subscore	−0.0069	0	124	−2.24	**0.027**
Age	−0.0295	0.01	71	−4.47	**<0.001**
Concomitant medication lorazepam	−0.5356	0.16	71	−3.31	**0.002**
Cognitive index					
Age	−0.0214	0	71	−5.03	**<0.001**
Concomitant medication lorazepam	−0.2476	0.1	71	−2.37	**0.020**

All values in bold are significant with $p < 0.05$.

8. Regarding single cognitive domains quetiapine was found to improve working memory, verbal memory, reaction quality and visual memory. Comparing quetiapine and haloperidol Purdon *et al*. found quetiapine superior regarding the improvement of several cognitive domains (Purdon *et al*., 2001). Other authors were able to confirm the beneficial influence of quetiapine on cognitive improvement (Good *et al*., 2002; Velligan *et al*., 2002).

Olanzapine was found to significantly improve working memory, verbal memory and visual memory. Meltzer and McGurk observed significant improvements in verbal learning and memory, verbal fluency, and executive function during olanzapine treatment.

Table 4. Regression analysis for the prediction for the course of cognition from baseline to week 8

	Estimate	Std. error	*t*-value	pr(>|*t*|)
Working memory				
PANSS negative subscore	−0.0216	0.0078	−2.77	**0.007**
PANSS positive subscore	−0.0171	0.0083	2.07	**0.041**
PANSS general psychopathology subscore	−0.0230	0.0067	−3.42	**0.001**
Treatment risperidone[a]	−0.1846	0.1456	−1.27	0.208
Treatment olanzapine[a]	−0.1531	0.1245	−1.23	0.222
Treatment aripiprazole[a]	−0.5366	0.1155	−4.65	**<0.001**
Verbal memory				
PANSS negative subscore	−0.0221	0.0092	2.39	**0.019**
Reaction quality				
PANSS general psychopathology subscore	−0.0309	0.0124	−2.48	**0.016**
Age	−0.0276	0.0110	−2.52	**0.015**
Concomitant medication lorazepam	0.5822	0.2560	2.27	**0.027**
Reaction time				
No explaining variables were found				
Executive function				
PANSS positive subscore	0.0091	0.0054	1.70	0.092
Age	−0.0049	0.0034	−1.42	0.156
Visual memory				
Age	0.0088	0.0046	1.94	0.055
Cognitive index				
PANSS positive subscore	0.0062	0.0042	1.47	0.143
PANSS negative subscore	0.0105	0.0040	2.61	**0.010**

All values in bold are significant with $p < 0.05$.

[a]Based on dummy coding quetiapine was used as reference medication thereby concurrently considered as potential influencing predictive variable. As risperidone, olanzapine and aripiprazole have negative signs their influence on cognition is significantly worse than the influence of the reference medication (in this case quetiapine). This indicates that quetiapine features the most favourable influencing profile.

DOI: 10.1002/hup

Improvements in verbal and visual memory have been confirmed by other authors (Cuesta *et al*., 2001; Smith *et al*., 2001). Comparing olanzapine, risperidone, clozapine and haloperidol regarding their effects on cognition olanzapine exhibited improvements in the general and attention domains but not more than the other antipsychotic drugs applied (Bilder *et al*., 2002).

A significant improvement in the cognitive domain reaction time was found during risperidone treatment. It should be kept in mind that only 17 patients were treated with risperidone which might explain why the improvement of several cognitive domains did not reach significance level. Comparing placebo, risperidone and clozapine Akdede *et al*. found significant improvements in both treatment groups in a variety of cognitive measures, however, with a significantly greater improvement in the placebo-augmented group (Akdede *et al*., 2006). In a recently published review article on oral and long-acting injectable risperidone and cognitive functioning the authors concluded that oral risperidone appears to be associated with improved functioning in cognitive domains (Houthoofd *et al*., 2008).

Regarding the treatment with aripiprazole a significant improvement of the domains reaction time and reaction quality was observed. There is very limited comparative literature on the influence of aripiprazole on cognition. Evaluating aripiprazole and neurocognition in stable outpatients Kern *et al*. found verbal learning and the general cognitive functioning to improve significantly during the treatment (Kern *et al*., 2006). In a case report Mucci and colleagues described cognitive enhancing effects during aripiprazole treatment compared to other second generation antipsychotics (Mucci *et al*., 2008).

Similar to other trials, we did not find evidence for an association of antipsychotic dosage and cognitive functioning (Klingberg *et al*., 2008). But there are reports that cognitive functioning strongly depends on antipsychotic dosage and also on the number of antipsychotics prescribed as Elie *et al*. described poorer cognitive functioning with increasing antipsychotic daily dose, interestingly at doses lower than previously thought (Elie *et al*., 2009).

However, discussing these results one should keep in mind that only randomized controlled trials and two different intervention strategies are adequate to show different treatment effects (Keefe *et al*., 2004). Also, interpreting the present results the influence of practice effects can not be disregarded. In one of the first trials examining cognitive improvement with second-generation antipsychotics in first-episode schizophrenia patients including healthy controls undergoing repeated testing the possibility that improvements in cognition might simply reflect practice effects was assessed (Goldberg *et al*., 2007). The authors found some of the improvements in cognition in the patient group to be related to practice effects.

Taking these aspects into account, we cannot conclude that the cognitive enhancement detected can be totally attributed to the treatment applied. To eliminate practice effects as much as possible, the neurocognitive tests in the study at hand were performed using different parallel versions at every assessment point. Caution is furthermore wanted as no healthy control group was included in the study design limiting further conclusions of the individual influence of the antipsychotic treatment applied. In addition, we do not know how many patients had a medication independent 'spontaneous' improvement as we have no placebo control included.

Influencing variable psychopathology

A lower PANSS negative subscore significantly influenced a favourable functioning in the cognitive domains working memory and reaction time and was furthermore significantly positive predictive for the domains working memory, verbal memory and visual memory. A lower PANSS positive subscore was only significantly predictive for one cognitive domain, namely working memory, whereas a lower PANSS general psychopathology subscore significantly influenced reaction quality and visual memory and was significantly positive predictive for reaction quality.

The PANSS general psychopathology subscore contains items on depression, fear as well as impaired concentration or active social avoidance and thereby resembles depressive and negative symptoms to a certain degree suggesting that depressive symptoms might influence reaction quality as well as visual and working memory. The prominent influence of negative and depressive symptoms on neurocognition in schizophrenia is in agreement with current literature (Brebion *et al*., 1997; Heydebrand *et al*., 2004; Holthausen *et al*., 1999; Hughes *et al*., 2003). Heydebrand *et al*. found the severity of negative symptoms to be associated with specific deficits in neuropsychological performance such as deficits in memory or psychomotor speed, which is in perfect agreement with the present results of the PANSS negative subscore significantly influencing and predicting working, verbal and visual memory (Heydebrand *et al*., 2004). Kohler *et al*. evaluated cognitive impairment in patients with schizophrenia comparing patients with and without depressive symptoms and

DOI: 10.1002/hup

related the main difference between these two groups in the domain of attention, namely the task of vigilance underlining the importance of depressive symptoms for cognitive impairments (Kohler *et al*., 1998). Mösner *et al*. were able to confirm this result as they also found depressive symptoms to significantly influence attention measure and memory measures, which also supports the present results (Moser *et al*., 2006). Interestingly, an association of subjective mood states and neurocognitive performance was furthermore found in a study by Halari *et al*. (2006). The authors even found the patient-rated symptoms predicting more cognitive domains than the clinician-rated symptoms suggesting that self-perceived negative mood states may be a better predictor of cognitive deficits than clinician-rated symptoms.

Regarding positive symptoms, some studies report associations between psychotic symptomatology and neurocognitive performance, whereas others have reported no relationship (Brazo *et al*., 2002; Penades *et al*., 2001; Strauss, 1993). In line with our results Bozikas *et al*. found an association between positive symptoms and working memory (Bozikas *et al*., 2004). Even though these correlations were modest, the authors suggest that psychopathology and cognitive deficits in schizophrenia are caused, at least, partially, by distinct pathophysiological processes. In a recent review, Dominguez *et al*. fit literature results in the simplistic but heuristically useful two-pathway model of psychosis, in which negative and disorganized symptoms are associated with the intermediary phenotype of neurocognitive impairment while the positive and affective dimensions are not (Dominguez *et al*., 2009).

Influencing variable age

Few studies of patients suffering from schizophrenia have investigated the effects of the patient's age using an extensive neuropsychologic battery (Fucetola *et al*., 2000). In the present analysis we found age to strongly influence cognition and to be a significant predictor as older patients scored significantly worse in the cognitive domains working memory, reaction quality, visual memory and executive function. The association between age and especially executive function has also been stated by other authors (Bhatia *et al*., 2009; Giovagnoli *et al*., 1996). The majority of studies of age-related neuropsychologic change found little evidence of cognitive decline (Chen *et al*., 1996; Mockler *et al*., 1997) which might be due to the fact that age-related differences in patients with schizophrenia may disappear when effects of normal aging are accounted for (Heaton *et al*., 1994). Examining the interaction of aging and neuropsychologic function comparing patients with schizophrenia and healthy controls Fucetola *et al*. found their results consistent with the literature as similar age effects were detected in patients and controls (Fucetola *et al*., 2000). However, the authors believe that their results support the hypothesis that a degenerative process may result in a more accelerated decline of some executive functions in older age schizophrenia patients, a hypothesis worthy of further study.

Influencing variable concomitant medication

In the present analysis, the concomitant application of lorazepam was found to significantly predict reaction quality in that sense that with greater lorazepam administration reaction quality decreased. Furthermore, the cognitive domains of visual memory and the cognition index were significantly influenced the same way. These results demonstrate that despite stopping lorazepam as concomitant medication 24 h before neurocognitive testing, due to a half-value period of 12–16 h, an influence of lorazepam on cognitive performance is still detectable. This result might not surprise keeping data on healthy subjects and benzodiazepines in mind which can end up in cognitive impairments and attention deficits (Vidailhet *et al*., 1999). As negative effects of anticholinergic medication on learning and memory have been demonstrated (Spohn and Strauss, 1989) the influence of anticholinergic medication for the course and development of cognition were furthermore analysed, yet without finding a significant influence. Evaluating changes in neuropsychological functioning in 108 patients with schizophrenia Jerrell and Ramirez did not find a significant result in their covariate analysis using anticholinergic medication (Jerrell and Ramirez, 2008). Unfortunately, further comparative data are limited. Klingberg *et al*. also complained that most studies do not control for the effect of different drugs administered such as concomitant medication (Klingberg *et al*., 2008).

STRENGTHS AND LIMITATIONS

Strengths of the present analysis are the comparison of four atypical antipsychotics and the matching study design of the different studies examined. Also, the same study registrars performed the ratings and the same measuring instruments were applied enhancing generalizability of the study results. However, it should be kept in mind that post-hoc analyses bear the risk of

DOI: 10.1002/hup

biasing the significance of clinical results (Moreno *et al*., 2009; Turner *et al*., 2008).

A limitation of present results is that no control group was included and that the improvements observed might at least partially be drawn back on practice results. The present study accounted for practice effects by using different parallel versions of the cognitive tests applied. Another limitation is that patients were not included in the present study if they had not responded to one of the applied antipsychotics in their medical history which might bias the results given that predominantly treatment responder were included.

Conclusion

Considered together, the results demonstrate an improvement of cognitive deficits in patients with an acute episode of schizophrenia regardless of the antipsychotic applied. Quetiapine was found to improve working memory significantly better than risperidone, olanzapine and risperidone. Also, negative and depressive symptoms, the patient's age, time point of treatment as well as the concomitant treatment applied were observed to significantly influence and predict neurocognition.

ACKNOWLEDGEMENTS

The study on quetiapine and risperidone was supported by AstraZeneca, the study on olanzapine and quetiapine by Lilly and the study on aripiprazole by Janssen-Cilag. M. Riedel has received research grants/support or has served as a consultant for AstraZeneca, Pfizer, Otsuka Pharma, Janssen-Cilag. In the context of investigator initiated trials, M. Riedel has received support from AstraZeneca and Pfizer. H.-J. Möller has received/is receiving research grants/support from, serves as a consultant or is on the advisory board for, or is a member of the speaker bureau for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Eisai, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck, Novartis, Organon, Pfizer, Sanofi Aventis, Sepracor, Servier, Wyeth. N. Müller has achieved support for research or honoraries from Affectis, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Cilag, Lilly Germany, Lundbeck, Pfizer Pharma, and Wyeth Pharma.

REFERENCES

Akdede BB, nil Yagcioglu AE, Alptekin K, *et al*. 2006. A double-blind study of combination of clozapine with risperidone in patients with schizophrenia: effects on cognition. *J Clin Psychiatry* **67**: 1912–1919 .

American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association: Washington DC.

Bhatia T, Garg K, Pogue-Geile M, Nimgaonkar VL, Deshpande SN. 2009. Executive functions and cognitive deficits in schizophrenia: comparisons between probands, parents and controls in India. *J Postgrad Med* **55**: 3–7.

Bilder RM, Goldman RS, Volavka J, *et al*. 2002. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. *Am J Psychiatry* **159**: 1018–1028.

Bozikas VP, Kosmidis MH, Kioperlidou K, Karavatos A. 2004. Relationship between psychopathology and cognitive functioning in schizophrenia. *Compr Psychiatry* **45**: 392–400.

Brazo P, Marie RM, Halbecq I, *et al*. 2002. Cognitive patterns in subtypes of schizophrenia. *Eur Psychiatry* **17**: 155–162.

Brebion G, Smith MJ, Amador X, Malaspina D, Gorman JM. 1997. Clinical correlates of memory in schizophrenia: differential links between depression, positive and negative symptoms, and two types of memory impairment. *Am J Psychiatry* **154**: 1538–1543.

Chen EY, Lam LC, Chen RY, Nguyen DG, Chan CK. 1996. Prefrontal neuropsychological impairment and illness duration in schizophrenia: a study of 204 patients in Hong Kong. *Acta Psychiatr Scand* **93**: 144–150.

Cording C. 1998. Conceptual aspects in development and implementation of basic psychiatric documentation. *Psychiatr Prax* **25**: 175–178.

Cuesta MJ, Peralta V, Zarzuela A. 2001. Effects of olanzapine and other antipsychotics on cognitive function in chronic schizophrenia: a longitudinal study. *Schizophr Res* **48**: 17–28.

Davidson M, Galderisi S, Weiser M, *et al*. 2009. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). *Am J Psychiatry* **166**: 675–682.

Dominguez MG, Viechtbauer W, Simons CJ, van OJ, Krabbendam L. 2009. Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. *Psychol Bull* **135**: 157–171.

Elie D, Poirier M, Chianetta J, Durand M, Gregoire C, Grignon S. 2009. Cognitive effects of antipsychotic dosage and polypharmacy: a study with the BACS in patients with schizophrenia and schizoaffective disorder. *J Psychopharmacol*.

Fahrmeir L, Kneib T, Lang S. 2007. Linear regression models. *Regression; Modelle, Methoden und Anwendungen*. Springer Verlag: Heidelberg; 59–188.

Fucetola R, Seidman LJ, Kremen WS, Faraone SV, Goldstein JM, Tsuang MT. 2000. Age and neuropsychologic function in schizophrenia: a decline in executive abilities beyond that observed in healthy volunteers. *Biol Psychiatry* **48**: 137–146.

Giovagnoli AR, Del PM, Mascheroni S, Simoncelli M, Laiacona M, Capitani E. 1996. Trail making test: normative values from 287 normal adult controls. *Ital J Neurol Sci* **17**: 305–309.

Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR. 1997. Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Arch Gen Psychiatry* **54**: 159–165.

Goldberg TE, Goldman RS, Burdick KE, *et al*. 2007. Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? *Arch Gen Psychiatry* **64**: 1115–1122.

Good KP, Kiss I, Buiteman C, *et al*. 2002. Improvement in cognitive functioning in patients with first-episode psychosis during treatment with quetiapine: an interim analysis. *Br J Psychiatry Suppl* **43**: s45–s49.

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

Gutbrod K, Cohen R, Mager B, Meier E. 1989. Coding and recall of categorized material in aphasics. *J Clin Exp Neuropsychol* **11**: 821–841.

Guy W. 1976. Clinical global impressions. *ECDEU Assessment Manual for Psychopharmacology*, National Institute of Mental Health, Rockville, MD (revised).

Halari R, Mehrotra R, Sharma T, Kumari V. 2006. Does self-perceived mood predict more variance in cognitive performance than clinician-rated symptoms in schizophrenia? *Schizophr Bull* **32**: 751–757.

Harvey PD, Green MF, McGurk SR, Meltzer HY. 2003. Changes in cognitive functioning with risperidone and olanzapine treatment: a large-scale, double-blind, randomized study. *Psychopharmacology (Berl)* **169**: 404–411.

Harvey PD, Patterson TL, Potter LS, Zhong K, Brecher M. 2006. Improvement in social competence with short-term atypical antipsychotic treat-

ment: a randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning. *Am J Psychiatry* **163**: 1918–1925 .

Hawkins KA. 1999. Memory deficits in patients with schizophrenia: preliminary data from the Wechsler Memory Scale-Third Edition support earlier findings. *J Psychiatry Neurosci* **24**: 341–347.

Heaton R, Paulsen JS, McAdams LA, *et al*. 1994. Neuropsychological deficits in schizophrenics. Relationship to age, chronicity, and dementia. *Arch Gen Psychiatry* **51**: 469–476.

Heaton RK, Gladsjo JA, Palmer BW, Kuck J, Marcotte TD, Jeste DV. 2001. Stability and course of neuropsychological deficits in schizophrenia. *Arch Gen Psychiatry* **58**: 24–32.

Heydebrand G, Weiser M, Rabinowitz J, Hoff AL, DeLisi LE, Csernansky JG. 2004. Correlates of cognitive deficits in first episode schizophrenia. *Schizophr Res* **68**: 1–9.

Hill SK, Bishop JR, Palumbo D, Sweeney JA. 2010. Effect of second-generation antipsychotics on cognition: current issues and future challenges. *Expert Rev Neurother* **10**: 43–57.

Holthausen EA, Wiersma D, Knegtering RH, Van den Bosch RJ. 1999. Psychopathology and cognition in schizophrenia spectrum disorders: the role of depressive symptoms. *Schizophr Res* **39**: 65–71.

Houthoofd SA, Morrens M, Sabbe BG. 2008. Cognitive and psychomotor effects of risperidone in schizophrenia and schizoaffective disorder. *Clin Ther* **30**: 1565–1589.

Hughes C, Kumari V, Soni W, *et al*. 2003. Longitudinal study of symptoms and cognitive function in chronic schizophrenia. *Schizophr Res* **59**: 137–146.

Jerrell JM, Ramirez PM. 2008. Changes in neuropsychological functioning following treatment with risperidone, olanzapine, and conventional antipsychotic medications. *Hum Psychopharmacol* **23**: 595–604.

Kay SR, Opler LA, Lindenmayer JP. 1988. Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Res* **23**: 99–110.

Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. 2004. The brief assessment of cognition in schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res* **68**: 283–297.

Keefe RS, Roitman SE, Harvey PD, *et al*. 1995. A pen-and-paper human analogue of a monkey prefrontal cortex activation task: spatial working memory in patients with schizophrenia. *Schizophr Res* **17**: 25–33.

Keefe RS, Sweeney JA, Gu H, *et al*. 2007. Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry* **164**: 1061–1071.

Kern RS, Green MF, Cornblatt BA, *et al*. 2006. The neurocognitive effects of aripiprazole: an open-label comparison with olanzapine. *Psychopharmacology (Berl)* **187**: 312–320.

Kirkpatrick B, Fenton WS, Carpenter WT, Jr, Marder SR. 2006. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull* **32**: 214–219.

Klingberg S, Wittorf A, Sickinger S, Buchkremer G, Wiedemann G. 2008. Course of cognitive functioning during the stabilization phase of schizophrenia. *J Psychiatr Res* **42**: 259–267.

Kohler C, Gur RC, Swanson CL, Petty R, Gur RE. 1998. Depression in schizophrenia: I. Association with neuropsychological deficits. *Biol Psychiatry* **43**: 165–172.

Lindenmayer JP, Khan A, Iskander A, Abad MT, Parker B. 2007. A randomized controlled trial of olanzapine versus haloperidol in the treatment of primary negative symptoms and neurocognitive deficits in schizophrenia. *J Clin Psychiatry* **68**: 368–379.

LoSasso GL, Rapport LJ, Axelrod BN, Reeder KP. 1998. Intermanual and alternate-form equivalence on the trail making tests. *J Clin Exp Neuropsychol* **20**: 107–110.

Mockler D, Riordan J, Sharma T. 1997. Memory and intellectual deficits do not decline with age in schizophrenia. *Schizophr Res* **26**: 1–7.

Moreno SG, Sutton AJ, Turner EH, *et al*. 2009. Novel methods to deal with publication biases: secondary analysis of antidepressant trials in the FDA trial registry database and related journal publications. *BMJ* **339**: b2981. DOI: 10.1136/bmj.b2981

Moser C, Krieg JC, Zihl J, Lautenbacher S. 2006. Attention and memory deficits in schizophrenia: the role of symptoms of depression. *Cogn Behav Neurol* **19**: 150–156.

Mucci A, Piegari G, Galderisi S. 2008. Cognitive-enhancing effects of aripiprazole: a case report. *Clin Pract Epidemol Ment Health* **4**: 24.

Penades R, Gasto C, Boget T, Catalan R, Salamero M. 2001. Deficit in schizophrenia: the relationship between negative symptoms and neurocognition. *Compr Psychiatry* **42**: 64–69.

Purdon SE, Malla A, Labelle A, Lit W. 2001. Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. *J Psychiatry Neurosci* **26**: 137–149.

Reitan RM. 1958. Validity of the trailmaking test as an indication of organic brain damage. *Percept Mot Skills* **8**: 271–276.

Riedel M, Muller N, Spellmann I, *et al*. 2007a. Efficacy of olanzapine versus quetiapine on cognitive dysfunctions in patients with an acute episode of schizophrenia. *Eur Arch Psychiatry Clin Neurosci* **257**: 402–412.

Riedel M, Spellmann I, Strassnig M, *et al*. 2007b. Effects of risperidone and quetiapine on cognition in patients with schizophrenia and predominantly negative symptoms. *Eur Arch Psychiatry Clin Neurosci* **257**: 360–370.

Schmidt M. 1996. *Rey Auditory Verbal Learning Test—A Handbook*. Western Psychological Services: Los Angeles.

Schuurman PR, Bruins J, Merkus MP, Bosch DA, Speelman JD. 2002. A comparison of neuropsychological effects of thalamotomy and thalamic stimulation. *Neurology* **59**: 1232–1239.

Smith RC, Infante M, Singh A, Khandat A. 2001. The effects of olanzapine on neurocognitive functioning in medication-refractory schizophrenia. *Int J Neuropsychopharmacol* **4**: 239–250.

Spohn HE, Strauss ME. 1989. Relation of neuroleptic and anticholinergic medication to cognitive functions in schizophrenia. *J Abnorm Psychol* **98**: 367–380.

Spreen O, Benton AL. 1965. Comparative studies of some psychological tests for cerebral damage. *J Nerv Ment Dis* **140**: 323–333.

Strauss ME. 1993. Relations of symptoms to cognitive deficits in schizophrenia. *Schizophr Bull* **19**: 215–231.

Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. 2008. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* **358**: 252–260.

Velligan DI, Newcomer J, Pultz J, *et al*. 2002. Does cognitive function improve with quetiapine in comparison to haloperidol? *Schizophr Res* **53**: 239–248.

Vidailhet P, Danion JM, Chemin C, Kazes M. 1999. Lorazepam impairs both visual and auditory perceptual priming. *Psychopharmacology (Berl)* **147**: 266–273.

Voruganti LP, Awad AG, Parker G, *et al*. 2007. Cognition, functioning and quality of life in schizophrenia treatment: results of a one-year randomized controlled trial of olanzapine and quetiapine. *Schizophr Res* **96**: 146–155.

Wiebel B, Happe A, Peikara F. 1995. *Das Neuropsychologische Diagnostikprogramm TESTBAT*. Psymed: Dulmen.

Wittorf A, Sickinger S, Wiedemann G, Klingberg S. 2008. Neurocognitive effects of atypical and conventional antipsychotic drugs in schizophrenia: a naturalistic 6-month follow-up study. *Arch Clin Neuropsychol* **23**: 271–282.

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

Woodward ND, Purdon SE, Meltzer HY, Zald DH. 2007. A meta-analysis of cognitive change with haloperidol in clinical trials of atypical antipsychotics: dose effects and comparison to practice effects. *Schizophr Res* **89**: 211–224.