Eur Arch Psychiatry Clin Neurosci (2007) 257:402–412 DOI 10.1007/s00406-007-0748-9

ORIGINAL PAPER

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Efficacy of olanzapine versus quetiapine on cognitive dysfunctions in patients with an acute episode of schizophrenia

Received: 12 December 2006 / Accepted: 3 May 2007 / Published online: 14 July 2007

Abstract Neurocognitive impairment is a core feature in the pathology of schizophrenia and considered to be relatively persistent towards psychopharmacological interventions. There are hints that atypical antipsychotics can influence neurocognitive dysfunctions more favorable than conventional compounds. But little is known about differences in efficacy on neurocognitive dysfunctions linked to the variety of receptor profiles of different atypical antipsychotics. This study compared the effects of the atypical antipsychotics quetiapine and olanzapine on cognitive function in patients with an acute episode of schizophrenia. Patients were randomized to receive quetiapine or olanzapine for 8 weeks. Cognitive function was assessed at baseline, week 4 and week 8. Efficacy was assessed weekly using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Improvement Scale (CGI). Tolerability was assessed each week using the Extrapyramidal Symptom Rating Scale (ESRS), the Barnes Akathisia Scale (BAS) and the Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU). In total, 52 patients were enrolled in the study. Data from the 33 patients who completed cognitive assessments at two or more time points out of three (baseline, Week 4 and Week 8) are analyzed here. Both quetiapine and olanzapine improved global cognitive index z-scores, however, this was more marked with quetiapine. Between-group comparisons showed significantly greater improvements in reaction quality/attention with quetiapine than olanzapine. Quetiapine and olanzapine produced significant improvements from baseline to week 8 in PANSS total and subscale scores. Both treatments were well tolerated, especially no EPS occurred during 8 weeks of treatment. Both quetiapine and olanzapine improved cognition; however, the improvement in cognitive index scores was more marked in patients receiving quetiapine. Furthermore, quetiapine produced a significantly greater improvement in reaction quality/attention than olanzapine.

Key words schizophrenia · atypical antipsychotics · cognitive improvement · quetiapine · olanzapine

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EAPCN 748

Introduction

More than 90 years ago Kraepelin and Bleuler described cognitive dysfunctions, especially disturbances of attention, as a core symptom of schizophrenia [6, 29]. They argued that cognitive symptoms, independently of acute or remittent episodes of schizophrenia, are featured by relatively constant and persisting characteristics.

Cognitive schizophrenic symptoms comprise numerous functional domains. At a recently held consensus conference (NIMH-MATRICS-Conference) participants found an agreement on typical deficits in seven main neurocognitive domains: working memory, attention/vigilance, verbal learning and memory, visual learning and memory, speed of processing, reasoning and problem solving and verbal comprehension. An eighth domain, social cognition, was added due to recent increased interest in this area and other evidence of its relevance for clinical trials

aiming to evaluate the impact of potential cognitive enhancers on cognitive performance and functional outcome [15]. The cognitive deficits in these described domains are mostly characterized by a moderate to severe state and seem to be relatively stable from the first episode up to the midlife of schizophrenic patients [19, 20]. In addition cognitive dysfunctions shall be relatively independent from the existence of other psychotic symptoms [22].

The relationship between positive and negative symptoms as well as neurocognitive dysfunctions have been investigated in reference to their etiologic importance. Hereafter there is a significant relationship between negative and cognitive symptoms taking their similarities in early incidence, course of disease and prognostic value for the outcome into account, while the overlap between positive and cognitive symptoms shall be more or less negligible [23].

Furthermore it has been shown that schizophrenic patients suffering from more pronounced negative symptoms were more affected by cognitive dysfunctions than schizophrenic patients without negative symptoms, healthy controls or patients with a bipolar disorder [18]. Positive symptoms are more fluctuating and more accessible towards an antipsychotic treatment. In addition positive symptoms shall influence the psychosocial outcome of the disorder to a lesser degree than negative or cognitive symptoms [3, 56, 58].

The effect of conventional antipsychotics, like haloperidol, on cognitive dysfunctions in schizophrenic patients is controversial [37]. An explanation of discrepant results may be the application of different dosages. While higher dosages of conventional antipsychotics seem to have none or even negative effects on cognitive functions, lower dosages have been shown to be accompanied by an amelioration of cognitive deficits [27, 14]. However, it has to be assumed that even lower dosages of conventional antipsychotics could induce extrapyramidal symptoms and consecutively lead to a deterioration of cognitive parameters [27].

In clinical studies with atypical antipsychotics like clozapine, olanzapine and risperidone, a favorable influence on cognitive dysfunctions could have been demonstrated [28, 35, 54]. Different from conventional antipsychotics, these effects seem to be more or less independent from improvements in psychopathology [4, 27, 40]. With regard to the severity of cognitive deficits in schizophrenic patients, which ranges between one or two standard deviations below the norm, atypical antipsychotics are even more effective than low dosed conventional antipsychotics [27]. Up to now only a few studies with a direct comparison of atypical antipsychotic effects on cognitive deficits have been performed. Thus these investigations are of major importance as the receptor binding profiles of individual atypical antipsychotics are characterized by a remarkable variety and could consecutively show differentiated effects on cognitive functions. Besides a rather selective blockade of mesolimbic dopaminergic receptors, a blockade of serotonergic 5-HT_{2A} receptors, without a nameable effect on the nigrostriatal system, seems to be relevant for an improvement of neurocognitive deficits. The blockade of serotonergic receptors shall lead to an increased dopaminergic activity in prefrontal cortex areas as well as to an improved dopaminergic transmission at Dopamin-D_1 receptors in the neocortex [39]. However, other study results cast doubt on the importance of a $5HT_{2A}$ antagonism as an assumption for an improvement of neurocognitive dysfunctions. They highlight the possibility of an advantageous influence on cognitive symptoms without a 5-HT_{2A} blockade [57] and emphasize that a high affinity to 5-HT_{2A} receptors could respectively be accompanied by a decrease of performances in visual recognition memory and planning abilities [51]. Nevertheless, there is a consensus on the negative influences of anticholinergic substances, as they are applied in the treatment of extrapyramidal symptoms, on memory functions [50]. It could be assumed that the total effect of a single atypical antipsychotic on cognitive functions can be considered as a net balance between positive and negative partial effects.

In a 2004 publicated meta analysis about cognitive factors in the treatment of schizophrenia Lewis et al. summarized as a broad consensus that atypical antipsychotics could improve neurocognitve deficits, both in patients considered to be resistent towards psychopharmacological interventions and in previously untreated patients. The current data would determine a very optimistic long-term prognosis [33]. The efforts in decoding new receptor effects of atypical antipsychotics like the antagonism at the 5-HT_6 receptor, which shall lead to an increase in dopamine and acetylcholine release in the prefrontal cortex and consecutively to an improvement of cognitive deficits [7, 45], should be enhanced in future investigations.

Methods

Patients

Inpatients aged 18–65 years were eligible to participate in the study. Patients with a DSM-IV diagnosis of schizophrenia, Clinical Global Impression scale score >4 and a PANSS total score >60 (Positive and Negative Symptom Scale [PANSS]) were eligible for inclusion. 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 enrollment. All patients gave written informed consent according to procedures approved by the ethics committee of the medical faculty of the University of Munich prior to study inclusion. The study was also approved by the ethics committee of the medical faculty of the University of Munich.

Study design

This was an investigator-initiated randomized, parallel-group, double-blind eight-week trial comparing the effects of quetiapine and olanzapine in patients with an acute episode of schizophrenia.

Table 1 Neurocognitive tests used to assess the six cognitive domains

Domain assessed	Test name	Variable measured
Working memory	Rey Auditory Verbal Learning, list 1 and 2, trial 1 (RAVLT) [43]	Working memory function
	Letter-number span sequencing task [11]	Auditory working memory
	Self ordered pointing task (SOPT) [16]	Visual working memory
Verbal memory	Rey Auditory Verbal Learning Test (RAVLT), list 1, trials 1–5, 6–8	Verbal declarative memory function
Reaction time and quality	Neurobat S—Short version [59]	Sustained attention and sensomotor flexibility tests
	Trails A test [42]	
Executive functions	Trails B test	General psychomotor function
	Verbal fluency and category fluency [49]	Category and letter fluency measures
Visual memory	Wechsler memory scale-revised [17]	Memory of non-verbal stimuli
	One point test [26]	Visuospatial working memory

Patients receiving previous, non-depot antipsychotic treatment underwent a 2–7 days washout period before randomization to reach baseline dopamine receptor occupancy levels and reduce the possibility of illness deterioration.

Treatment

A fixed-dose initiation schedule was used during the first week of treatment according to the applicable guidelines of the manufacturer at the initiation of the study.

Quetiapine was initiated at 50 mg and olanzapine at 10 mg on Day 1. Within the first 7 days quetiapine was titrated up to 600 mg and olanzapine up to 15 mg/day. Thereafter, study medication was flexibly dosed according to clinician's judgment between 400–800 mg/day quetiapine and 10–20 mg/day olanzapine. In the event that a study participant did not respond effectively to the maximum dose, the patient was withdrawn from the study. Anticholinergic medication (biperidene hydrochloride ≤8 mg/day) was administered to treat EPS. Concomitant lorazepam (<4 mg) and zopiclone (<15 mg) were allowed to counteract agitation and sleep problems. Lorazepam and zopiclone had to be discontinued at least 24 h prior to neurocognitive testing to assure an unaffected result.

Neurocognitive test battery

The neurocognitive tests were chosen to represent a range of reliable and validated tests, which have been used in similar trials. The entire battery (Table 1) took between 90–120 min to complete. With the exception of Neurobat-S short version, the One-point test, and Self-ordered-pointing task (SOPT), we used three different parallel versions of the neurocognitive tests at the three test sessions. The tests were grouped into six cognitive domains: reaction time, reaction quality/attention, executive functions, working memory, verbal learning and memory, and visual memory. A global cognitive index was constructed through the addition and averaging of the z-scores from individual cognitive domains.

The neurocognitive test battery was administered prior to randomization and following 4 and 8 weeks of treatment. During the initial assessment, premorbid intelligence was ascertained using the Multiple Choice Word Test-B (MWT-B) [30]. Results from this vocabulary test correlate with 'crystallised intelligence', which remains stable during adulthood and is relatively independent of concurrent psychopathology.

Clinical assessments

Assessments were carried out on a weekly basis by medically trained study staff and included the monitoring of vital signs, laboratory check-ups, and evaluation of tolerability and patient psychopathology. Additionally, at the end of Weeks 4 and 8, ECGs to monitor cardiac safety and body weight measures were recorded. Adherence to treatment was assessed by weekly pill counts.

The efficacy and tolerability of quetiapine and olanzapine treatment was assessed using a number of standardized rating scales. The primary measure of psychopathology was the PANSS. In addition, the Clinical Global Improvement Scale (CGI) was used. Tolerability was assessed using the Extrapyramidal Symptom Rating Scale (ESRS), the Barnes Akathisia Scale (BAS) and the Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU).

Adverse events were recorded as additional indicators of tolerability throughout the trial.

Statistical analysis

Data analyses were carried out using SPSS (version 14.0 for windows) software. Data were analyzed using the Mann–Whitney *U*-Test to analyze between group differences in response over the duration of the study. The Fisher's exact test was used to analyze between group differences in nominal parameters and adverse events. Students paired *t*-test was used to compare the means (baseline vs. endpoint) for each treatment group and p values ≤0.05 were considered statistically significant. Lacking efficacy- and tolerability data were approximately evaluated by using the Last-Observation-Carried-Forward (LOCF)—procedure. In consideration of the fact that this study exhibits a hypothesis-generating rather than a confirmatory character a correction for multiple testing was renounced in order to identify tendential significant correlations as well.

Results

Patients

About 52 patients with an acute schizophrenic episode participated for 8 weeks in this double-blind, randomized trial. Efficacy, tolerability, and cognitive function data from the 33 patients who completed cognitive assessments at least at two or more time points out of three (baseline, week 4 and week 8) were analyzed here.

Prior to inclusion a total of 21 patients were antipsychotically untreated at least for 4 weeks. Eight patients were treated with conventional antipsychotics and seven patients were treated with atypical antipsychotics. In six patients with a previous conventional antipsychotic treatment (four patients with haloperidol, one with flupentixole and one with chlorprothixene) and in two previously risperidone treated patients the medication was discontinued due to extrapyramidal side effects, in the remaining four

Table 2 Demographic and baseline characteristics

	Quetiapine (n = 16)	Olanzapine (n = 17)	T	P
Sex (m/f)	10/6	11/6		1.00
Age (years)	36.69 (11.71)	34.47 (11.60)	0.55	0.59
Age of onset (years)	28.25 (7.10)	29.76 (9.00)	−0.54	0.60
Duration of illness (years)	8.44 (10.11)	4.71 (6.22)	1.29	0.21
Weight (kg)	79.45 (16.02)	75.90 (9.70)	0.80	0.45
PANSS total score	100.31 (13.93)	90.06 (20.79)	1.65	0.11
Positive subscore	24.44 (5.12)	22.94 (6.65)	0.72	0.47
Negative subscore	23.13 (7.26)	21.35 (7.66)	0.68	0.50
Global subscore	52.75 (6.79)	45.76 (10.73)	2.22	0.03
CGI	5.63 (0.62)	5.35 (0.70)	1.18	0.25
ESRS score	0.25 (1.00)	1.00 (2.48)	−1.13	0.27
BAS score	0.00 (0.00)	0.35 (1.46)	−0.97	0.34
UKU score	1.44 (4.50)	0.06 (0.20)	0.24	0.22
MWT-B	26.56 (7.99)	25.06 (8.00)	0.54	0.59

patients with a previous atypical antipsychotic treatment (two patients with risperidone, one with ziprasidone and one with amisulpride) the medication was discontinued due to lack of efficacy. No patient received previous depot antipsychotic treatment. The mean wash-out time was 4.7 ± 3.5 days. There were no significant differences between pre- and untreated patients with respect to efficacy measures including neuropsychological test results, PANSS or CGI scores.

The mean age of the patients treated with quetiapine (n = 16) was 36.69 (11.71) years and 34.47 (11.59) years of the patients treated with olanzapine (n = 17; P = 0.59). Except the PANSS global score, there were no significant differences according to age of onset, duration of illness, MWT-B or efficacy and tolerability scores at baseline between both treatment groups (Table 2). The mean doses during 8 weeks of treatment were 586.86 mg (169.12 mg) for quetiapine and 15.82 mg (5.44 mg) for olanzapine.

About 17 patients treated with quetiapine and 15 patients treated with olanzapine terminated the study prior to the endpoint. In both treatment groups the most frequently indicated reason for a dropout was a missing efficacy of the compound. In the quetiapine as well as in the olanzapine group one patient dropped out due to intolerable side effects and four patients were lost to follow-up or withdrew their informed consent.

Efficacy

Cognitive functioning

Neurocognitive tests were performed at baseline, week 4 and week 8. Different test results were transformed to z-values for direct comparison and thematically similar tests were assigned to six cognitive domains.

Patients in both treatment groups improved in nearly all cognitive domains during eight weeks of treatment (Fig. 1). Patients treated with quetiapine improved significantly in working (z-scores baseline to endpoint: −0.06 ± 0.17 to 0.03 ± 0.16; $P < 0.05$), verbal (−0.06 ± 0.29 to 0.04 ± 0.08; $P < 0.001$) and visual memory (−0.01 ± 0.07 to 0.03 ± 0.05; $P < 0.01$) as well as in reaction quality/attention (−0.04 ± 0.13 to 0.07 ± 0.08; $P < 0.01$) from baseline to week 8. During the last four weeks of the study this improvement could have been extended in verbal and visual memory and reaction quality/attention. In working memory no further improvement could have been observed. After a decrease in executive functions up to week 4, caused by a slight worsening in three items of category fluency (acceptable and incorrect words as well as repetitions), patients treated with quetiapine improved slightly during the last 4 weeks, although this improvement was not significant compared with baseline levels. Patients treated with olanzapine improved continuously in all cognitive domains from baseline to week 8, although this improvement was only significant in working (z-scores baseline to endpoint: −0.06 ± 0.17 to 0.03 ± 0.19; $P < 0.001$), verbal (−0.09 ± 0.22 to 0.002 ± 0.06; $P < 0.05$) and visual memory (−0.04 ± 0.11 to 0.004 ± 0.08; $P < 0.01$). There was a significant difference between both treatment groups, as the improvement in reaction quality/attention was more pronounced in patients in the quetiapine group (z-scores baseline to endpoint: −0.04 ± 0.13 to 0.07 ± 0.08) than in patients treated with olanzapine (−0.07 ± 0.36 to 0.005 ± 0.15; $P < 0.05$).

To assure a direct comparison of the results of both treatment groups mean z-values of individual cognitive domains were summarized in a global cognitive index (Fig. 2). In both treatment groups neurocognitive indices improved significantly. Despite that the overall improvement in patients treated with quetiapine was more pronounced (z-scores baseline to endpoint: −0.03 ± 0.09 to 0.02 ± 0.08; $P < 0.001$) than in patients treated with olanzapine (−0.04 ± 0.12 to 0.01 ± 0.07; $P < 0.05$), this difference was not found to be statistically significant.

In Table 3 results of individual neuropsychological tests are presented. Patients treated with quetiapine experienced significant improvements in 16 individual neuropsychological tests from baseline to endpoint of the study, whereas patients treated with olanzapine improved in seven tests. In five tests (Auditory verbal learning test, trials 1–5, correct responses, Duration of attention, Sensomotoric trial, errors and correct responses, Verbal fluency, acceptable words) the improvement from baseline to endpoint was significantly better in the quetiapine treatment group than in patients treated with olanzapine.

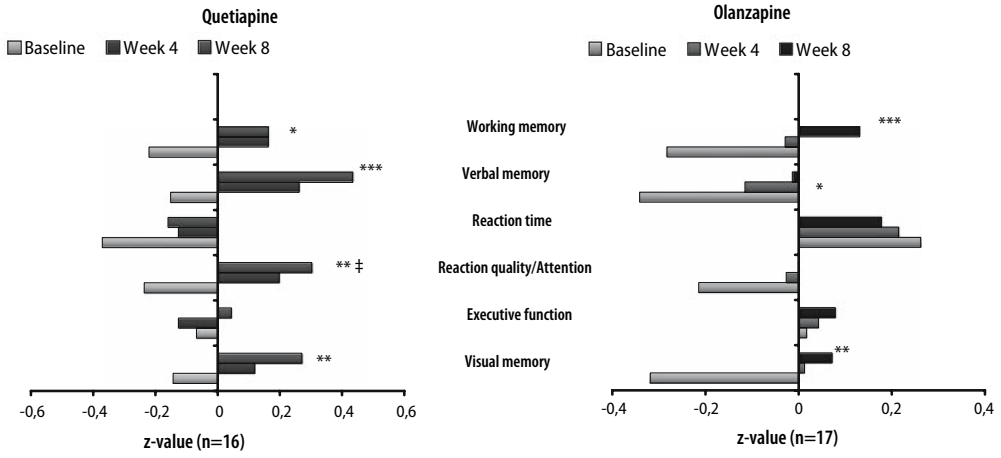

Fig. 1 Mean z-values of six neurocognitive domains at baseline, week 4 and week 8. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ vs. baseline, paired *t*-test; ‡$P < 0,05$ vs. olanzapine, Mann–Whitney *U*-test

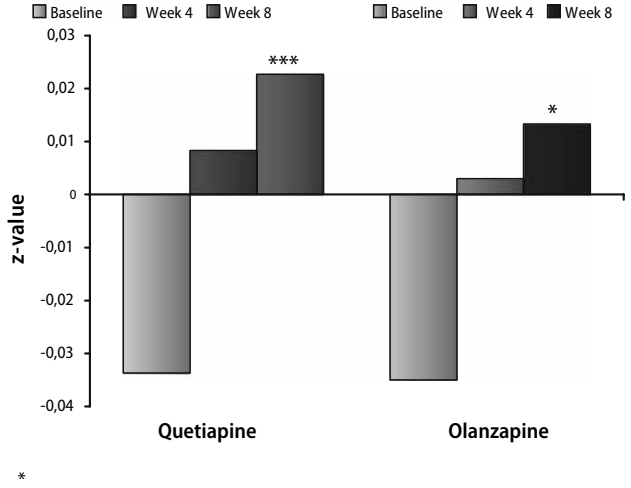

Fig. 2 Mean global cognitive indices at baseline, week 4 and week 8. *$P < 0.05$; ***$P < 0.001$ vs. baseline; paired *t*-test

Positive and negative syndrome scale (PANSS)

In both treatment groups significant improvements in PANSS total and subscale scores could be observed from baseline to end of week 8 (Fig. 3). In patients treated with quetiapine the reduction of PANSS total scores from baseline to endpoint was more pronounced (21.50 ± 23.39; $P < 0.001$, paired *t*-test) than in the olanzapine treatment group (17.88 ± 20.71; $P < 0.001$, paired *t*-test). However, there were no statistically significant differences in PANSS total and subscale score improvements between both treatment groups.

Clinical global impression (CGI)

The global severity of illness was evaluated according to the Clinical Global Impression Scale. It is subdivided into two different subscales, the Clinical Global Severity scale (CGI-S) and the Clinical Global Improvement scale (CGI-I). In the CGI-S patients treated with quetiapine improved from 5.63 (0.62) points at baseline to 4.06 (1.00) points at week 8 ("markedly ill" to "moderately ill"), whereas patients in the olanzapine group improved from 5.35 (0.70) points at baseline to 3.94 (1.20) points at week 8 ("markedly ill" to "moderately ill"). Concerning the efficacy of psychopharmacological treatment according to the CGI-S there were no significant differences between both treatment groups ($P = 0.652$).

Corresponding to the CGI-S patients in both treatment groups improved significantly in the CGI-I scale (from "no change" to "much improved"). Group differences were not significant ($P = 0.437$).

Tolerability

Extrapyramidal symptoms (EPS)

Extrapyramidal symptoms were assessed weekly by the Extrapyramidal Symptom Rating Scale (ESRS). A decrease in mean ESRS scores could have been observed during eight weeks of treatment in both treatment groups. The mean ESRS score at baseline was 0.25 (1.0) points in quetiapine treated patients and 1.0 (2.5) in the olanzapine group. During eight weeks of treatment no additional increase of ESRS scores could have been observed. On the contrary mean ESRS scores decreased to zero in both treatment groups at endpoint.

The incidence of akathisia was assessed by the Barnes Akathisia Scale (BAS).

At baseline mild akathisia was only present in the quetiapine treatment group [$n = 1$, mean BAS score = 0.35 (1.5)]. At endpoint neither in patients treated with quetiapine nor in the olanzapine treatment group akathisia could have been observed.

Table 3 Results of individual neuropsychological tests

	Quetiapine (n = 16)			Olanzapine (n = 17)			Between-group-difference
	Baseline Mean (SD)	Week 4 Mean (SD)	Week 8 Mean (SD)	Baseline Mean (SD)	Week 4 Mean (SD)	Week 8 Mean (SD)	P
Category							
Working memory							
Auditory verbal learning test							
List 1, trial 1, correct responses	5.0 (1.2)	6.8 (1.5)	**7.6 (2.9)	5.0 (1.4)	5.7 (1.3)	***6.8 (1.6)	0.606
List 2, trial 1, correct responses	4.9 (2.1)	4.9 (2.5)	4.9 (2.6)	5.2 (1.5)	4.8 (1.8)	5.0 (2.2)	0.817
Letter-number span	13.3 (3.2)	14.5 (2.9)	14.3 (3.6)	12.3 (4.1)	12.7 (3.4)	13.4 (3.3)	0.444
Self ordered pointing tasks 1–4, errors	2.0 (1.1)	1.4 (1.0)	1.4 (1.1)	2.1 (0.9)	1.4 (1.0)	**1.4 (1.2)	0.411
Verbal memory							
Auditory verbal learning test							
List 1, trials 1-5 (learning trials)	41.0 (11.5)	48.8 (10.7)	***51.3 (13.1)	40.3 (8.9)	43.5 (8.3)	43.7 (8.8)	**0.019**
List 1, trial 6 (interference recall)	7.9 (4.5)	9.9 (3.6)	**10.1 (3.7)	6.9 (2.6)	7.9 (2.7)	*8.1 (2.7)	0.292
List 1, trial 7 (delayed recall), correct	6.9 (4.0)	9.6 (4.0)	***9.9 (4.3)	6.0 (2.6)	7.7 (2.9)	**8.4 (3.1)	0.345
Recognition Form, correct recognitions	12.06 (3.40)	12.75 (2.18)	*13.00 (3.01)	11.47 (2.76)	10.9 (3.3)	11.8 (2.1)	0.127
Recognition Form, correct rejections	33.31 (2.21)	33.00 (2.61)	33.75 (1.91)	33.12 (1.69)	33.71 (1.26)	33.59 (1.58)	0.790
Reaction time							
Sensomotoric 1–4 (ms)	546.89 (76.93)	495.63 (72.32)	*503.36 (74.41)	467.01 (63.86)	486.09 (74.51)	489.82 (87.91)	0.102
Duration of attention 1–3 (ms)	498.13 (66.55)	473.49 (52.97)	*465.14 (44.50)	443.58(45.59)	460.43 (40.01)	464.39 (45.21)	**0.023**
Trail making test A (s)	41.94 (16.60)	35.63 (11.93)	**34.44 (9.67)	34.71 (11.12)	31.06 (14.72)	30.59 (15.16)	0.709
Reaction quality/attention							
Sensomotoric trial 1–4							
Errors	2.30 (1.48)	1.27 (0.84)	**0.92 (0.85)	2.24 (3.31)	2.12 (2.61)	1.88 (2.65)	**0.028**
Correct responses	21.89 (2.04)	23.16 (1.25)	**23.81 (0.94)	22.54 (3.74)	22.57 (3.09)	22.88 (3.13)	**0.017**
Duration of attention trial 1–3							
Errors	8.08 (5.86)	5.47 (4.37)	*4.90 (3.83)	9.98 (12.42)	7.37 (8.04)	7.94 (7.85)	0.204
Correct responses	230.83(10.37)	237.20 (9.40)	*238.19 (8.55)	231.53 (16.30)	234.35 (12.88)	232.75 (12.43)	0.118
Executive functions							
Verbal fluency, acceptable words	42.13 (17.87)	45.94 (21.27)	**49.81 (22.04)	42.29 (16.09)	43.29 (14.11)	43.47 (15.52)	**0.014**
Verbal fluency, repetitions	2.25 (4.09)	1.75 (2.59)	1.38 (1.86)	1.06 (1.09)	1.65 (1.27)	1.53 (1.77)	0.444
Verbal fluency, incorrect words	0.63 (0.89)	0.63 (0.81)	0.63 (1.09)	0.59 (0.94)	0.47 (1.01)	0.35 (0.49)	0.763
Category fluency, acceptable words	36.00 (10.46)	34.88 (10.02)	37.19 (11.12)	35.88 (9.73)	33.82 (9.02)	34.65 (8.97)	0.276
Category fluency, repetitions	0.38 (0.50)	1.25 (1.77)	0.69 (1.14)	0.24 (0.56)	0.24 (0.56)	0.29 (0.47)	0.736
Category fluency, incorrect words	0.13 (0.34)	0.25 (0.77)	0.31 (1.01)	0.12 (0.33)	0.18 (0.39)	0.18 (0.39)	0.958
Trail making test B (s)	86.81 (31.43)	72.88 (22.79)	*68.31 (20.98)	91.06 (59.36)	69.94 (40.52)	**68.71 (35.38)	0.929
Visual memory							
Wechsler visual memory scale							
Immediate reproduction	31.50 (5.75)	34.69 (4.39)	**34.94 (3.92)	31.35 (5.78)	32.94 (4.09)	33.29 (3.95)	0.382
Delayed reproduction	23.88 (11.52)	29.06 (7.64)	**31.25 (6.12)	22.59 (11.06)	28.56 (8.71)	*28.71 (9.88)	0.533
One point test							
Immediate reproduction	12.83 (4.19)	13.22 (3.25)	11.92 (3.34)	12.22 (2.72)	12.22 (2.22)	11.58 (2.51)	0.510
Delayed reproduction	16.33 (4.00)	15.62 (3.92)	16.50 (4.95)	23.62 (15.57)	19.43 (9.86)	*19.91 (11.81)	0.204

Bold type indicates a significant advantage of quetiapine over olanzapine ($P < 0.05$; Mann–Whitney U-test). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs. baseline (paired t-test)
The different trial numbers listed above indicate the versions of the tests used in this study

The presence of extrapyramidal symptoms as well as akathisia at baseline can be ascribed to a medication with conventional antipsychotics prior to inclusion.

Udvalg for Kliniske Undersogelser side effect rating scale (UKU)

Most of the adverse events associated with a possible causal relationship to quetiapine or olanzapine are summarized within the UKU domain "Psychiatric".

In this domain patients treated with olanzapine had a significant higher score in the subitem "sedation" within the first week of treatment [1.12 (0.86) vs. 0.5 (0.73); $P = 0.034$] than patients in the olanzapine group. This effect has also been observed after 5 weeks of treatment [0.92 (0.86) vs. 0.27 (0.47); $P = 0.036$]. Besides patients in the olanzapine group had a significant higher score in the UKU subitem "increased sleep duration" than patients treated with quetiapine at week 5 [0.62 (0.77) vs. 0; $P = 0.015$]. There were no significant differences between both treatment groups in the remaining individual items or domains scores.

Most distinctive scores in the causality item (mean causality score ≥ 0.2) has been found in "concentration difficulties", "asthenia/increased fatiguability", "sleepiness/sedation", "increased duration of sleep", "orthostatic dizziness" and "weight gain".

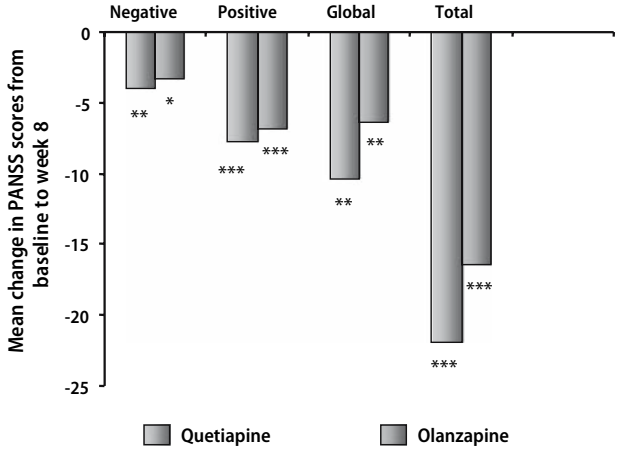

Fig. 3 Improvement in PANSS subscores from baseline to week 8; *$P < 0.05$; **$P < 0,01$; ***$P < 0,001$ vs. baseline; paired *t*-test

Table 4 Adverse events

Adverse event	Quetiapine *n* (%) ($n = 16$)	Olanzapine *n* (%) ($n = 17$)	*P*
Headache	4 (25%)	3 (17.7%)	1.00
Sedation	10 (62.5%)	13 (76.5%)	0.79
Dizziness	4 (25%)	2 (11.8%)	0.66
Obstipation	8 (50%)	2 (11.8%)	0.15
Weight gain	8 (50%)	8 (47.1%)	1.00

P = between treatment comparison (Fisher's exact test, two-tailed)

Adverse events

Adverse events spontaneously reported by patients were documented throughout the study and summarized in Table 4. Both compounds were characterized by a similar side effect profile. In both treatment groups sedation and weight gain (defined as an increase of more than 7% compared to baseline at the endpoint of the study) were the most frequently reported adverse events.

The quantifiable weight gain after 8 weeks of treatment was 3.28 (3.17) kg in quetiapine treated patients and 3.76 (2.77) kg in the olanzapine group ($P = 0.779$). A similar number of patients in both treatment groups suffered from headache and dizziness. In quetiapine treated patients obstipation was reported more frequently than in the olanzapine group, but the difference was not statistically significant.

There were no serious adverse events observed throughout the duration of the study.

Comedication

Patients with an acute episode of schizophrenia often suffer from tension or anxiety. Thus lorazepam could have been administered additionally up to 4 mg/day. At baseline patients in the quetiapine group received 1.71 (0.92) mg lorazepam/day and patients treated with olanzapine 1.9 (2.0) mg lorazepam/day ($P = 0.723$). The mean dose of the whole treatment-period was 1.16 (0.72) mg lorazepam/day for patients in the quetiapine group and 1.22 (1.28) mg/day for patients treated with olanzapine ($P = 0.853$).

For treatment of EPS 4 mg biperidene could have been administered, but neither at baseline nor during the following 8 weeks of atypical antipsychotic treatment any patient received biperidene.

Discussion

For this eight-week, randomized, double-blind study 52 patients with an acute episode of schizophrenia were recruited. Patients were treated with either olanzapine or quetiapine, which are both similar to clozapine according to their chemical structure.

Patients treated in this study improved in test results of several neurocognitive domains during 8 weeks of treatment with quetiapine or olanzapine. However, there was a significant difference in the neurocognitive domain reaction quality/attention between both treatment groups, since patients treated with quetiapine improved to a significantly greater degree in this subdomain than patients of the olanzapine treatment group. Besides quetiapine was tendentially superior to olanzapine according to the improvement in an overall cognitive index, although differences were not statistically significant.

The finding of an improvement in different cognitive domains during a treatment with atypical antipsychotics is consistent with the literature. In a study of Purdon et al. [41] it could have been demonstrated that quetiapine was superior to haloperidol in improving several cognitive domains [41]. Velligan et al. [53] obtained similar results during a six-month treatment-period with quetiapine versus haloperidol. Significant improvements in global cognitive and executive functions as well as in verbal memory in patients treated with quetiapine could have been achieved [53]. In an open-label study of Good et al. with patients suffering from a first schizophrenic episode significant improvements in several cognitive domains like attention, verbal fluency and executive functions during a treatment with quetiapine were reported [13]. The observed significant improvements in executive function in the literature couldn't be replicated neither in our current study nor in a study with a similar design comparing the effects of risperidone and quetiapine on cognition in patients with schizophrenia and predominantly negative symptoms [44]. In fact, test results of patients in the cognitive domain executive function decreased after four weeks of treatment with quetiapine, caused by a slight worsening in three items of category fluency (acceptable and incorrect words as well as repetitions). However, compared to baseline levels, a slight improvement in executive functions could have been

observed in both treatment groups after eight weeks. Possibly the missing significance of improvement or even the decrease in executive function in quetiapine treated patients after four weeks could have been correlated to side effects which are connected to receptor profiles of both compounds. Due to their relatively high affinity to H_1-receptors quetiapine and olanzapine possess antihistaminergic properties and can induce a sedating effect, especially at the beginning of treatment, which may lead to a worsening of neurocognitive functions [47]. Compared to quetiapine, olanzapine exhibits a higher affinity to H_1-receptors. This could explain why more patients treated with olanzapine suffered from sedation/tiredness according to the results of the UKU scale as well as to the summary of adverse events in this investigation. Furthermore it could have been observed that sedating effects caused by olanzapine had a more pronounced long-lasting effect than those reported for quetiapine. However, quetiapine was taken in the form of two single doses during the day, whereas olanzapine was administered in the evening. This could have led to the decrease in executive functions observed in quetiapine patients at week 4. This effect seems to be reversible since patients in the quetiapine group increased in executive functions up to week 8 which indicates that quetiapine may cause a sedating effect only at the beginning of treatment.

Besides our study cannot be directly compared to other results from the literature since patients in this study carried higher PANSS positive subscores at baseline than patients in the above mentioned study of Good et al. which may explain the delay of improving executive functions.

The treatment with olanzapine resulted in significant improvements in working, verbal and visual memory and less pronounced improvements in remaining cognitive domains and the general cognitive index compared to quetiapine. In a multi-center study of Purdon et al. treatment with olanzapine was associated with an improvement in motor functions, attention, executive functions, visuo-spatial perception and less pronounced improvements in reasoning and verbal fluency [40].

Meltzer und McGurk [35] reported about 21 patients treated with olanzapine in a six-week study and experienced significant improvements in verbal learning and memory, verbal fluency, and executive function, but not attention, working memory, or visual learning and memory. Improvements in verbal and visual memory could have been confirmed in other publications [8, 48]. In a 14 week, double-blind, multi-center study of Bilder et al. olanzapine, risperidone, clozapine and haloperidol were compared with regard to their effects on neurocognition in patients with chronic schizophrenia or schizoaffective disorder. Patients treated with olanzapine exhibited improvements in the general and attention domains but not more than that observed with other treatments. Patients treated with risperidone exhibited improvement in memory that was superior to that of both clozapine and haloperidol. Clozapine yielded improvement in motor function but not more than in other groups [4].

In our study quetiapine was significantly superior to olanzapine with regard to improvements in reaction quality/attention. In individual test results patients treated with quetiapine improved significantly more in auditory verbal learning test (trial 1–5), duration of attention (reaction time), sensomotoric trial 1–4 (errors and correct responses) and verbal fluency (acceptable words) than patients in the olanzapine group.

All mentioned cognitive variables are considered as important prognostic factors for long-term psychosocial outcome of patients [52]. In a longitudinal analysis of 40 schizophrenic patients Velligan et al. investigated if certain neurocognitive dysfunctions could serve as predictors for special social or professional skills after one to three and a half years of treatment. They found correlations between the cognitive domain verbal memory and all investigated parameters of social outcome, between attention and social skills as well as between executive functions and professional skills.

The neurocognitive domain reaction quality/attention in our study contained a psychometric evaluation of general attention and vigilance items as well as sensomotoric skills, measured by the neuropsychologic diagnostic programme TESTBAT developed by Wiebel et al. [59]. In the study of Velligan et al. results in this cognitive domain were correlated with long-term social skills of the patients [52].

The significant advantage of quetiapine against olanzapine with regard to improvement in reaction quality/attention could be explained by the different receptor affinities of the two compounds. Olanzapine exhibits a higher affinity to dopaminergic, histaminergic and muscarinergic receptors, whereas quetiapine is characterized by a higher affinity to adrenergic α_1/α_2-receptors.

Compared to olanzapine, quetiapine exhibits a lower affinity to dopaminergic D_2-receptors. EPS did not occur in both treatment groups during eight weeks of treatment. Low ESRS scores at baseline were caused by treatment with typical antipsychotics prior to inclusion and decreased to zero throughout the study. Therefore EPS cannot be considered for differences in efficacy between both treatment groups.

A higher affinity to dopaminergic D_2-receptors with an adjunctive slower dissociation from the receptor shall lead to a decrease in dopaminergic transmission [25]. Thus neurocognitive dysfunctions presumably are associated with a reduction of dopaminergic activity in the prefrontal cortex, this mechanism of action could contribute to a consecutive impairment of neurocognitive functions and explain why quetiapine, with its rather low affinity to D_2-

receptors, carried out a more favorable effect on these cognitive symptoms than olanzapine.

An antagonism at serotonergic $5HT_{2A}$- and dopaminergic-D_2-receptors combined with a high $5HT_{2A}/D_2$ quotient, as it is realized in many atypical antipsychotics, shall implicate a more pronounced efficacy on neurocognitive dysfunctions [9, 34]. Compared to quetiapine, olanzapine exhibits a higher affinity to both receptors. However, both compounds differ only marginally with regard to their $5HT_{2A}/D_2$-quotient, so that the observed differences in efficacy cannot be attributed to this context. However, Tyson et al. found different effects of atypical antipsychotics on neurocognitive dysfunctions which depended on their affinity to $5HT_{2A}$-receptors [51].

By contrast the necessity of a serotonergic mechanism of action as an assumption of improvement of neurocognitive or negative symptoms was questioned by Wagner et al. who performed an eight-week, double-blind, randomized controlled trial of olanzapine versus amisulprid [57]. Both compounds had a similar effect on neurocognitive dysfunctions. Compared to olanzapine, amisulprid exhibits no clinical relevant affinity to serotonergic receptors and was found to be tendentially superior towards olanzapine in improving neurocognitive symptoms. Authors concluded that a combined $5\text{-}HT_{2A}/D_2$ receptor blockade may not be an imperative assumption of a positive effect on cognition. The "atypical" features of amisulpride and other substituted benzamides may also result from the pro-dopaminergic effect mediated by blocking of presynaptic D_2 autoreceptors. Blockade of these receptors leads to increased dopamine output into the striatum (reduction of EPS), maintaining a high rate of D_3/D_2 receptor blockade in the thalamus and temporal cortex. The additionally increased level of dopamine transmission in the prefrontal cortex could be responsible for the positive effect on negative and cognitive symptoms [32, 38].

Results of previous studies suggest a possible relationship between a blockade of muscarinergic receptors and a negative influence on cognition [28, 55]. Healthy probands showed restricted skills in repeating a word list after administration of scopolamin, a non-selective antagonist at cholinergic receptors [10, 36].

Cognitive dysfunctions are considered to be independent from psychopathology and shall be relatively resistant towards psychopharmacological interventions [12]. Besides atypical antipsychotics with a higher affinity to muscarinergic receptors, like clozapine, shall deteriorate cognitive functions as a result of their anticholinergic properties. Meanwhile it has been well established that atypical antipsychotics can have a beneficial influence on neurocognitive dysfunctions, but little is known about the efficacy profiles of different compounds [39].

Based on a study of Arnsten et al., who found a positive effect of α_1/α_2-adrenergic compounds on cognition in animal models [2], actual studies confirm that an increase in adrenergic transmission in the prefrontal cortex seems to be associated with an increase of dopaminergic activity and can contribute to a general improvement in cognitive functions of schizophrenic patients [1].

In a study of Hertel et al. it could be demonstrated that an additional administration of the α_2-antagonist idazoxan to a treatment with the D_2/D_3-antagonist racloprid increased dopamine release in the prefrontal cortex of rodents [21].

Compounds with an antagonistic impact at α_1-receptors may probably have a protecting effect towards an increased release of adrenergic substances caused by stress. Birnbaum et al. could demonstrate that stress induced cognitive dysfunctions could have been improved by infusion of urapidil, an α_1-antagonist [5]. Most atypical antipsychotics dispose of both mechanisms to different degrees. Quetiapine exhibits a higher affinity to adrenergic receptors than olanzapine. Apart from the lower affinity to histaminergic or muscarinergic receptors in comparison to olanzapine, this could be part of an explanation for the observed superior effect on neurocognitive dysfunctions in quetiapine treated patients.

With regard to psychopatholgy a significant improvement could be obtained within both groups in all efficacy parameters. Quetiapine was tendentially superior to olanzapine in improving PANSS and CGI subscores. This is consistent with a result of Sacchetti et al. who found an improvement in PANSS total scores of 34% for quetiapine, 30% for olanzapine and 29% for patients treated with risperidone in a 16-week randomized comparative study [46].

By contrast the results of a meta analysis of Leucht et al. showed an inferior effect of quetiapine against olanzapine in the treatment of global schizophrenic symptoms, compared to the conventional antipsychotic haloperidol [31].

There are several limitations to our study; the sample size was comparatively small and exhibits a hypothesis-generating rather than a confirmatory character. About 32 patients terminated our trial prior to study endpoint. Of these 17 patients were treated with quetiapine and 15 patients were in the olanzapine treatment group. As a main drop-out reason lack of efficacy was documented and occurred predominantly during the titration- and early treatment-phase. The acute schizophrenic episode was reflected by the relatively high PANSS scores at baseline. For treatment of tension and anxiety lorazepam could be administered up to a daily dose of 4 mg. In some cases this dosage was probably not sufficient during the titration and wash-out-period in order to compensate psychopathologic fluctuations. Similar drop-out rates with comparable high PANSS scores at baseline have been observed in the accreditation study of aripiprazole which have been tested against haloperidol and placebo [24]. In this study drop-out

quotas were 45% in the placebo (n = 106), 33% in the 15 mg aripiprazole (n = 102), 41% in the 30 mg aripiprazole (n = 102) and 40% in the haloperidol treatment group (n = 104).

Another possible limitation of our study was the presence of antipsychotic pre-medication in 12 patients prior to inclusion. Although all patients underwent a two to seven days washout period before randomization to reach baseline dopamine receptor occupancy levels, antipsychotics, especially conventional agents, can influence neurocognitive functioning in patients. As there were no significant differences in efficacy variables including neurocognitive test results, PANSS or CGI scores between antipsychotically pre- and untreated patients this influence seems to be rather negligible.

As a conclusion our study results confirm the importance of further elucidation of atypical antipsychotic efficacy on neurocognitive dysfunctions with regard to different receptor profiles.

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