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ORIGINAL PAPER

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Effects of risperidone and quetiapine on cognition in patients with schizophrenia and predominantly negative symptoms

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Abstract Evidence suggests that neurocognitive impairment is a key factor in the pathology of schizophrenia and is linked with the negative symptoms of the disease. In this study the effects of the atypical antipsychotics quetiapine and risperidone on cognitive function in patients with schizophrenia and with predominantly negative symptoms were compared. Patients were randomly assigned to double-blind treatment with quetiapine or risperidone for 12 weeks. Cognitive function was assessed at baseline, Week 6 and Week 12. Efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS) at baseline, Week 6 and Week 12. Extrapyramidal side-effects were assessed each week using the Simpson-Angus Scale (SAS), adverse events were recorded as additional indicators of tolerability throughout the trial. In total, 44 patients were enrolled in the study. Data from the 34 patients who completed cognitive assessments at two or more time points out of three (baseline, Week 6 and Week 12) are analysed here. Quetiapine improved significantly global cognitive index z-scores at both Week 6 ($p < 0.001$ vs. baseline) and Week 12 ($p < 0.01$ vs. baseline), whereas risperidone improved significantly global cognitive index z-scores at Week 12 ($p < 0.05$). Between-group comparisons at Week 6 showed significantly greater improvements in working memory and verbal memory with quetiapine than risperidone ($p < 0.05$) and a significantly greater improvement in reaction quality/attention with quetiapine than risperidone at Week 12 ($p<0.05$). Quetiapine and risperidone produced significant improvements from baseline in PANSS total ($p<0.001$) and subscale scores at Week 12. Significant improvements in SANS total score were also seen in both the quetiapine ($p < 0.001$) and risperidone ($p < 0.01$) groups at Week 12 compared with baseline. SAS scores, measuring the incidence of extrapyramidal side-effects, were higher in patients receiving risperidone compared with those receiving quetiapine, and significant differences were seen at Weeks 3, 4, 5 and 7. Both quetiapine and risperidone improved cognition according to changes in cognitive index scores from baseline to Week 12. These results suggest that quetiapine and risperidone provide valuable treatment options for patients with schizophrenia with predominantly negative symptoms. Also, the improvements in cognition following treatment with quetiapine and risperidone may enhance long-term outcomes for these patients.

Key words atypical antipsychotics · cognitive improvement · randomised clinical study · parallel-group study

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Introduction

Neurocognitive impairment has been viewed as a key factor in schizophrenia pathology. Close to a century ago, Kraepelin and Bleuler were among the first clinicians to include impaired cognitive processes as core features in their descriptions of schizophrenia [7, 46]. Over the past decades, a wealth of new empiric evidence associating specific cognitive impairments with schizophrenia has accumulated [50], with cur-

rent estimates suggesting that two-thirds of patients with schizophrenia have impaired cognition [58] with the remaining 'cognitively normal' patients likely to have experienced a decline in their cognitive function prior to onset of their illness.

Cognitive deficits, which lead to subtle early academic impairments, may be present prior to the first clear-cut psychotic episode and seem to remain stable at least over the early course of schizophrenia [2, 18]. These deficits have been observed to remain stable in ambulatory patients with schizophrenia regardless of changes in clinical state [29]. However, deterioration of cognition over time has been proposed to result from a cumulative interaction between early neurodevelopmental brain insults and neurodegeneration that occurs after the onset of the illness [43]. Importantly, the neurocognitive performance of patients with schizophrenia is closely correlated with several key outcome domains such as the development of new social skills and the ability to function independently in the community. Furthermore, neurocognitive performance is currently viewed as a limiting factor for treatment success and rehabilitation [16, 44, 56]. In this way, performance in various neurocognitive subdomains including executive functions, memory, and attention may differentially and independently contribute to the long-term course of schizophrenia [19].

Lifetime functional impairment and neurocognitive abilities, indicated by measures such as social functioning, have also been associated with negative symptoms of schizophrenia [1, 11, 12, 68]. Along with cognitive performance, negative symptoms are one of the most informative long-term prognostic outcome factors for patients with schizophrenia [67]. The positive symptoms of schizophrenia are thought to be more easily treated through psychopharmacological intervention (Green et al. 22] than either negative or cognitive symptoms [25], and thus, may arguably affect outcome to a lesser extent.

Additionally, patients with a preponderance of negative symptoms may show a generalized cognitive deficit [30]. However, the interrelation of cognitive deficits and negative symptoms appears to be relatively small, accounting for about 10–15% of overall variance [20].

The cognitive deficits associated with schizophrenia are not necessarily persistent, underlying deficits, as described in several naturalistic studies [6, 39]. A combination of pharmacotherapy with atypical antipsychotic medication along with behavioural compensatory approaches may provide considerable benefits to patients with schizophrenia [31]. Cognitive improvement may ameliorate some of the difficult-to-treat negative symptoms, which supports the theory that there is partial overlap in the neurobiological processes of these symptoms [30].

The introduction of atypical antipsychotics has improved the treatment of schizophrenia. In comparison with conventional antipsychotics, atypical antipsychotics have advantages in certain important outcome areas; efficacy against both positive and negative symptoms [4, 34] and a reduction in the incidence of extrapyramidal symptoms (EPS) and tardive dyskinesia [10, 51]. However, it is indicated in a recent meta-analysis that low-potency conventional antipychotics might not induce more EPS than new generation antipsychotics, but new generations drugs, as a group, were moderately more efficacious than low-potency conventional antipsychotics [49]. Moreover Leucht et al. found that not all atypical antipsychotics exhibited a superior efficacy on negative symptoms in comparison to haloperidol [48]. As there was only one study comparing the efficacy of quetiapine and haloperidol on negative symptoms included into the analysis, these results should be constricted [3].

It has been shown in several studies that atypical antipsychotics demonstrate greater efficacy against neurocognitive deficits, termed 'neurocognitive advantage' [23] and several studies have reported improvements in cognition after switching patients from conventional to atypical antipsychotics [6, 39, 70]. In a recent long-term study comparing the effects of olanzapine and low-dose haloperidol in first-episode psychosis both antipsychotic agents appeared to improve neurocognition, but there was a significantly greater benefit in favour of olanzapine at Weeks 12 and 24 [40, 41]. In a one-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenic patients neurocognition significantly improved in all treatment groups according to a composite score up to the endpoint with no significant between-group difference [42]. Additional post hoc analyses of the individual cognitive domains suggested that risperidone and olanzapine were more likely to provide significant improvement in specific areas of cognitive function.

To date, there have only been a limited number of studies directly comparing the efficacy of different atypical antipsychotics on cognitive impairment. Besides the above mentioned study of Keefe et al., Harvey et al. recently conducted a randomized, double-blind comparison of quetiapine vs. risperidone for social competence, social cognition, and neuropsychological functioning [26]. They found that scores on the performance-based measure of social competence significantly improved with both treatments, as did a number of aspects of neuropsychological performance. There were no overall differences between the treatments in their impact on social competence and neuropsychological performance. In another randomized, double-blind, flexible-dose, 8-week study the efficacy and tolerability of quetiapine vs. risperidone in the treatment of schizophrenia were compared [76]. It has been found that both agents improved cognitive and social functioning to a similar degree.

Such investigations would be of major importance given that the receptor-binding profiles of individual atypical agents differ considerably. Improvements in cognitive symptoms seem to require the selective blockade of serotonergic 5-HT_{2A} receptors and mesolimbic dopaminergic receptors, without a definitive effect on the nigrostriatal dopaminergic system. Thus, blockade of serotonergic receptors is proposed to strengthen dopaminergic transmission in the prefrontal cortex resulting in increased activity at dopamine D_1 receptors in the neocortex [59]. However, a number of recent studies have challenged the importance of 5-HT_{2A} antagonism in improving neurocognitive symptoms [72], emphasising instead the significance of the weaker affinity (loose binding concept) of some atypical antipsychotics for dopamine D_2 receptors [35, 36].

In many clinical studies cognitive symptoms are significantly related to negative symptoms, but no clear association was found between positive symptoms and neurocognitive deficits [5, 8, 64, 71]. Similar to cognitive dysfunctions, negative symptoms often precede the first psychotic episode; they usually show, however, a more pronounced progression during the course of disease [45, 54, 73].

Hawkins et al. [28] demonstrated that patients with schizophrenia and negative symptoms had significantly reduced cognitive function compared with patients without negative symptoms. Both syndromes are considered to be more resistant to psychopharmacological interventions and affect the psychosocial outcome to a greater degree than positive symptoms [5, 71, 74].

To date, no comparative trial has focused on the improvement in cognitive functions with atypical antipsychotics for patients with schizophrenia who have predominantly negative symptoms. In order to investigate the possibility that atypical antipsychotics have favourable effects on cognitive impairment and negative symptoms we conducted a randomised, double-blind, clinical trial comparing two well-established atypical antipsychotics, risperidone and quetiapine. Whereas both agents are characterized by a combined antagonism at D_2- and $5HT_{2A}$-receptors, risperidone exhibits a more potent affinity to both receptors. Due to their different receptor profiles we hypothesized that risperidone and quetiapine could influence neurocognitive functioning in different ways with a more or less favourable effect on a global cognitive index and on individual cognitive domains.

Methods

Patients

Outpatients and hospitalised patients aged 18–65 years were eligible to participate in the study (Study number D1441C09007 5077-9007). Patients with a DSM-IV diagnosis of schizophrenia, Clinical Global Impression Severity scale score ≥4, predominance of negative symptoms (Positive and Negative Symptom Scale [PANSS] Negative subscale ≥21, and at least 1 point higher than positive subscale) were eligible for inclusion. Exclusion criteria included: substance abuse, dependence or intoxication, suicidal tendencies, significant medical history (head trauma, epilepsy, meningoencephalitis), 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 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. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Study design

This was an investigator-initiated, randomised, parallel-group, double-blind, 12-week trial comparing the effects of quetiapine and risperidone in patients with schizophrenia and with predominantly negative symptoms. Patients receiving previous, non-depot antipsychotic treatment underwent a 2- to 7-day washout period before randomisation.

Treatment

A fixed-dose initiation schedule was used during the first week of treatment according to the specific manufacturers' guidelines. 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 Days 6 and 7. Thereafter, study medication was flexibly dosed according to the clinician's judgment between 400–800 mg/day quetiapine and 4–8 mg/day risperidone. 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 ≤ 8 mg/day) was administered if EPS were present at inclusion to the study or in case of a new incidence during the treatment phase. Concomitant lorazepam (<4 mg) and zopiclone (<15 mg) were allowed to counteract agitation and sleep problems and 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 and120 min to complete. 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 averaging of the z-scores from individual cognitive domains.

The neurocognitive test battery was first administered at baseline and again following 6 weeks and 12 weeks of treatment. During the initial assessment, premorbid intelligence was ascertained using the Multiple Choice Word Test-B (MWT-B) [47]. 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 2, 6 and 12, electrocardiograms (ECG) to monitor cardiac safety and body weight measures were recorded. Adherence to treatment was assessed by weekly pill counts.

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) [62]	Working memory function
	Letter-Number Span Sequencing Task [15]	Auditory working memory
	Self-Ordered Pointing Task (SOPT) [24]	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 [75]	Sustained attention and sensomotor flexibility tests
	Trails A Test [60]	
Executive functions	Trails B Test	General psychomotor function
	Verbal Fluency and Category Fluency [66]	Category and letter fluency measures
Visual memory	Wechsler Memory Scale-Revised [27]	Memory of non-verbal stimuli
	One Point Test [38]	Visuospatial working memory

The efficacy of quetiapine and risperidone treatment was assessed using a number of standardised rating scales. The primary measure of psychopathology was the PANSS. In addition, the Scale for the Assessment of Negative Symptoms (SANS) was used to further evaluate negative symptoms.

Extrapyramidal side-effects were assessed using the Simpson-Angus Scale (SAS). Adverse events were recorded as additional indicators of tolerability throughout the trial.

Statistical analysis

Data analyses were carried out using SPSS (version 13.0 for windows) software. Data were analysed using an univariate analysis of variance (ANCOVA) with two factors, one of them as repeated measurement, and was used to analyse differences between both treatment groups in time course during the duration of the study. The MWT-B, and baseline scores of PANSS negative symptoms and age at study entry were used as covariates throughout as there were significant differences at baseline in these variables. Additionally, the significant differences at baseline in SANS alogia, avolition/apathy and attention scores were included in the analysis of group differences within SANS subscales. Student's t-test was used to compare the means of baseline characteristics and weekly SAS scores between both treatment groups. The Fisher's exact test was used to analyse between group differences in nominal variables. Paired t-tests were used to compare the means (baseline vs. endpoint) within each treatment group and p-values ≤ 0.05 were considered statistically significant. Missing values were estimated by using the last observation carried forward (LOCF) method.

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

In total, 44 patients were enrolled in the study. Ten patients were excluded from the cognitive analysis, as they terminated the study prior to the second cognitive assessment at Week 6. Efficacy, tolerability, and cognitive function data from the 34 patients who completed cognitive assessments at two or more time points out of three (baseline, Week 6, and Week 12) are analysed here. Twenty of these were pre-treated prior to study inclusion with various non-depot atypical and conventional antipsychotics, 14 were untreated at the time of study inclusion. Of the 10 patients who withdrew from the study prior to Week 6, 4 were randomised to receive quetiapine and 6 to receive risperidone. In the quetiapine group, 2 withdrew due to lack of efficacy and 2 withdrew consent. In the risperidone group, 2 withdrew due to intolerable side effects, 3 withdrew due to lack of efficacy and 1 patient withdrew consent. There were no significant differences between these 10 patients excluded from the cognitive analysis compared to the remaining 34 patients according to demographic or other baseline characteristics. The flow of participants through each stage of the study, including patients withdrawn after the second neurocognitive assessment at Week 6, is shown in Table 2. The results from efficacy and tolerability assessments of all patients enrolled in the overall study have been presented previously [63].

Table 2 Flow of participants throughout the study[a]

Sex	Group	Day of Termination	Reason
M	Q	5	4
F	Q	70	3
M	Q	35	2
F	Q	70	4
F	Q	56	3
M	Q	42	4
F	Q	56	2
F	Q	21	4
M	Q	8	2
F	R	28	2
F	R	42	1
M	R	35	1
M	R	14	2
M	R	35	1
M	R	70	2
F	R	56	4
F	R	7	2
M	R	28	4
M	R	77	2

Sex: M = Male, F = Female; Group: Q = Quetiapine, R = Risperidone
Day of Termination: Number of days the patient remained in the study
Reason: 1 = Side-Effects, 2 = Lack of Efficacy, 3 = Lost to Follow-Up, 4 = Consent withdrawn.
[a] Only randomly assigned patients who terminated the study prior to week 12 are presented here

The majority of patients (79%) had a diagnosis of either paranoid (N = 15) or disorganised schizo-

Table 3 Patient demographics and clinical characteristics

	Quetiapine (N = 19)	Risperidone (N = 15)	T	p-value
Mean (SD) age, years	29.2 (10.7)	39.6 (12.4)	−2.62	0.01
Male/female, N	13/6	8/7		0.48[a]
Mean (SD) dose at endpoint, mg/day	569.2 (205.7)	5.1 (1.4)		
Mean (SD) duration of illness, years	3.3 (3.8)	2.3 (15.1)	0.260	0.80
PANSS scores at baseline (mean [SD])				
Positive subscale	19.1 (6.6)	21.7 (7.3)	−0.61	0.54
Negative subscale	30.7 (6.2)	25.2 (7.2)	2.40	0.02
Global subscale	52.7 (9.1)	49.8 (10.9)	0.86	0.40
Total	101.8 (14.9)	94.8 (17.2)	1.27	0.21
SANS scores at baseline (mean [SD])				
Affective blunting	18.3 (7.9)	13.7 (8.7)	1.64	0.11
Alogia	13.0 (6.3)	8.1 (5.4)	2.40	0.02
Avolition-apathy	12.1 (3.5)	9.6 (3.3)	2.08	0.05
Anhedonia-asociality	15.7 (4.0)	13.9 (4.7)	1.17	0.25
Attention	7.4 (3.2)	5.3 (3.0)	1.88	0.07
Total	66.3 (22.1)	50.6 (20.4)	2.13	0.41
Mean (SD) MWT-B	22.6 (8.9)	28.0 (5.8)	−2.05	0.05

[a] Fisher-Exact-Test

phrenia (N = 12). The remaining patients were diagnosed with either schizophrenia of catatonic (N = 1), residual (N = 2), or undifferentiated type (N = 1); or schizoaffective disorder (N = 3). The mean (SD) age of patients receiving risperidone was significantly greater (39.6 [12.4] years) than those receiving quetiapine (29.2 [10.7] years) [p = 0.012] (Table 3). The mean (SD) age of onset in the risperidone group was significantly later (37.3 [19.9] years) than in the quetiapine group (26 [11.2] years) [p = 0.044]; however, duration of illness was similar. A comparison of the MWT-B scores at baseline showed patients receiving risperidone had significantly higher scores than those receiving quetiapine (28 and 22.6, respectively; p < 0.05).

The mean dose at Week 6 was 570.6 mg/day for quetiapine and 5.1 mg/day for risperidone and at Week 12 the mean dose was 569.2 mg/day for quetiapine and 5.1 mg/day for risperidone. Five patients in the risperidone and eight patients in the quetiapine group required concomitant lorazepam for tension/agitation which developed during the study. The mean (SD) dose of concomitant lorazepam required was not significantly different between both groups (quetiapine group 0.43 [0.81] mg; risperidone group 0.2 [0.51] mg; p = 0.420).

Cognitive functioning

At baseline, patients receiving quetiapine had lower MWT-B scores than those receiving risperidone (22.6 vs. 28.0, p = 0.049). The scores from the individual neurocognitive tests are shown in Table 4 [15, 24, 27, 38, 60, 62, 66, 75]. Treatment with both quetiapine and risperidone improved global cognitive index z-scores relative to baseline during the 12-week study period (Fig. 1). This improvement was statistically significant in patients taking quetiapine at both Week 6 (p < 0.001) and at Week 12 (p < 0.01; however, the improvement relative to baseline in patients taking risperidone was only statistically significant at Week 12 (p < 0.05).

Patients receiving quetiapine showed statistically significant improvements in three of the six tested cognitive subdomains at Week 12 relative to baseline: working memory (p < 0.001), verbal memory (p < 0.001), and reaction quality/attention (p < 0.01) (Fig. 2). Patients receiving risperidone showed statistically significant improvement from baseline at Week 12 in working memory (p < 0.05), verbal memory (p < 0.01), reaction time (p < 0.01) and visual memory (p < 0.01). When the two treatment groups were compared at Week 6 of the study, quetiapine showed a significant advantage over risperidone in improving working memory (p < 0.05) and verbal memory (p < 0.05). At Week 12 there was a statistically significant difference in reaction quality/attention (p < 0.05) between the two groups with quetiapine-treated patients showing an improvement in this domain, while patients treated with risperidone deteriorated. There were no other statistically significant between-group differences for any of the cognitive assessments employed in this study at Week 12 (Fig. 2).

Efficacy

Patients receiving quetiapine had higher mean baseline PANSS negative scores in comparison with patients treated with risperidone (30.7 vs. 25.2, p = 0.022). In addition, patients receiving quetiapine had higher mean baseline SANS total scores in comparison with patients treated with risperidone (66.3 vs. 50.6, p = 0.041). Following 12 weeks of treatment, significant improvements (p ≤ 0.01) in PANSS total and subscale scores were seen in both treatment groups (Fig. 3).

Table 4 Results of individual neuropsychological tests at baseline, Week 6 and Week 12

Category	Quetiapine (n = 19)			Risperidone (n = 15)			Between-difference[a]
	Baseline Mean (SD)	Week 6 Mean (SD)	Week 12 Mean (SD)	Baseline Mean (SD)	Week 6 Mean (SD)	Week 12 Mean (SD)	p
Working memory							
Auditory verbal learning test							
List 1, trial 1, correct responses	4.95 (1.75)	7.21 (2.94)**	9.42 (2.74)***	5.13 (1.55)	5.93 (1.91)	7.60 (3.23)**	**0.048**
List 2, trial 1, correct responses	5.11 (2.13)	5.53 (2.17)	5.26 (2.31)	5.13 (1.69)	4.93 (1.87)	5.29 (1.68)	0.756
Letter-number span	12.58 (4.31)	12.89 (5.21)	12.79 (5.60)	13.64 (4.07)	12.47 (2.88)	13.87 (3.46)	0.339
Self-ordered pointing tasks 1-4, errors	7.26 (4.52)	5.53 (3.55)*	5.16 (3.85)*	7.73 (3.17)	8.40 (5.14)	8.67 (6.00)	**0.042**
Verbal memory							
Auditory verbal learning test							
List 1, trials 1-5 (learning trials), correct responses	41.68 (12.55)	50.84 (12.52)***	57.05 (11.59)***	40.60 (12.19)	44.13 (13.43)	51.64 (15.89)*	0.117
List 1, trial 6 (interference recall), correct responses	8.47 (3.13)	11.74 (2.40)***	12.53 (1.84)***	8.73 (3.77)	9.27 (4.45)	10.00 (4.49)	**0.008**
List 1, trial 7 (delayed recall), correct responses	8.89 (3.37)	10.79 (2.94)**	11.58 (2.52)**	8.00 (4.16)	8.80 (4.52)	10.14 (4.49)*	0.174
Recognition Form, correct recognitions	12.95 (2.07)	13.58 (1.54)	13.95 (1.39)*	12.07 (2.55)	12.00 (3.21)	12.86 (2.82)	0.161
Recognition Form, correct rejections	34.11 (1.05)	34.16 (1.26)	34.26 (1.28)	34.13 (1.19)	34.40 (0.83)	34.43 (1.02)	0.891
Reaction time							
Sensomotoric 1–4 (ms)	509.21 (93.08)	503.11 (61.52)	507.54 (82.97)	519.42 (148.96)	514.15 (71.81)	505.20 (74.49)	0.431
Duration of attention 1–3 (ms)	434.70 (40.04)	430.93 (43.14)	429.56 (38.66)	459.93 (42.87)	448.22 (42.45)	456.34 (42.29)	0.109
Trail making test A (s)	41.53 (24.28)	31.84 (14.60)**	30.32 (13.12)**	40.67 (18.80)	36.20 (10.26)	33.80 (10.89)	0.447
Reaction quality/attention							
Sensomotoric trial 1–4							
Errors	2.66 (2.62)	1.28 (1.23)*	1.30 (1.44)*	1.74 (1.55)	1.93 (1.86)	2.63 (2.69)	0.205
Correct responses	21.09 (4.54)	23.49 (1.35)*	23.37 (1.51)	21.07 (6.10)	22.80 (1.83)	21.98 (2.70)	0.317
Duration of attention trial 1–3							
Errors	9.32 (9.32)	5.23 (3.88)*	3.77 (3.03)*	7.71 (5.02)	9.04 (6.57)	8.47 (6.15)	**0.019**
Correct responses	228.32 (14.80)	236.14 (8.13)*	237.44 (8.31)*	231.11 (11.34)	228.47 (14.90)	228.69 (14.44)	**0.039**
Executive functions							
Verbal fluency, number of acceptable words	41.32 (18.82)	43.32 (15.20)	44.47 (16.11)	40.87 (10.62)	41.27 (13.51)	40.93 (14.20)	0.059
Trail making test B (sec)	105.95 (77.20)	79.21 (43.68)**	73.58 (42.67)**	91.27 (48.07)	79.73 (28.73)	78.00 (32.85)	0.308
Visual memory							
Wechsler visual memory scale							
Immediate reproduction	32.37 (7.90)	34.21 (5.99)	33.89 (5.82)	31.13 (8.27)	33.20 (6.86)	33.93 (7.48)*	0.330
Delayed reproduction	28.47 (9.88)	32.89 (8.01)**	33.00 (7.13)*	29.20 (8.42)	30.00 (10.99)	31.13 (10.82)	0.287
One point test							
Immediate reproduction	12.77 (2.443)	14.84 (5.01)*	13.73 (4.28)	14.01 (5.05)	13.01 (3.83)	12.58 (2.83)	0.136
Delayed reproduction	18.34 (5.56)	19.55 (6.43)	19.18 (8.37)	18.55 (8.98)	16.07 (5.75)	16.85 (5.57)	0.622

[a]Between treatment difference using Week 12 data. Bold type indicates a significant advantage of quetiapine over risperidone ($p < 0.05$)
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ for within-treatment group difference vs. baseline
The different trial numbers listed above indicate the versions of the tests used in this study

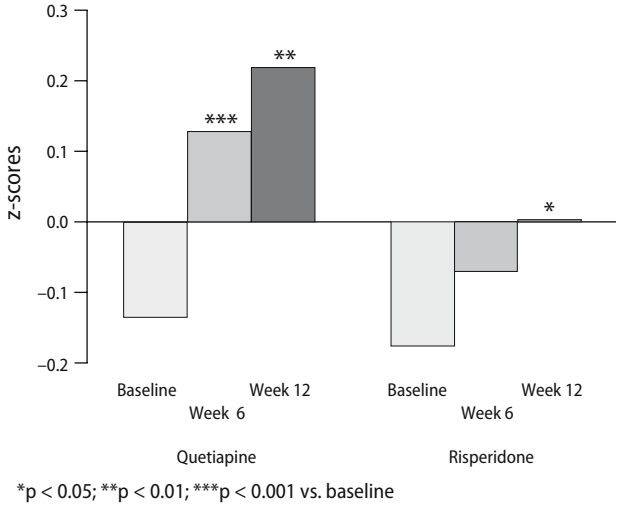


Fig. 1 Mean global cognition index z-scores at baseline, Week 6 and Week 12

SANS total scores improved in both the quetiapine ($p < 0.001$) and risperidone ($p < 0.01$) groups at Week 12 compared with baseline (Fig. 4). At Week 12 there was no statistically significant between-group difference in SANS total scores. Quetiapine significantly improved the affective blunting and alogia subscale scores relative to baseline ($p < 0.001$ and $p < 0.001$, respectively), compared with risperidone which did not elicit a significant improvement in these items relative to baseline over the 12-week period (Fig. 4).

Tolerability

The most frequent adverse events occurring in more than 5% of patients are summarised in Table 5. Baseline SAS scores were 0.3 for each treatment group. However, patients receiving risperidone had significantly greater scores at Weeks 3, 4 ($p < 0.05$), 5 ($p < 0.01$) and 7 ($p < 0.05$) compared with those patients treated with quetiapine (Fig. 5); this indicates an increased incidence and severity of EPS in patients

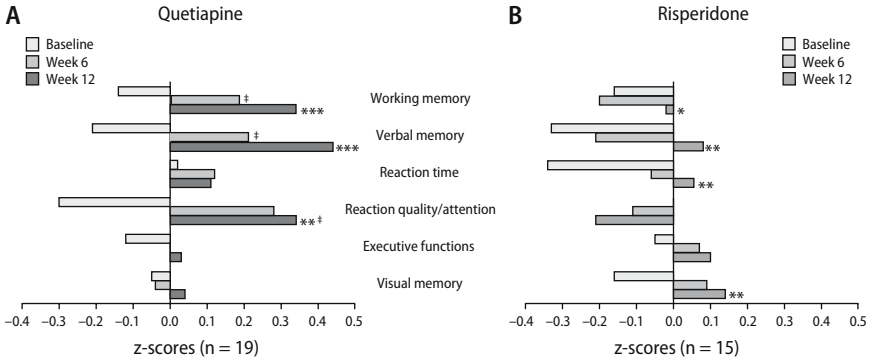
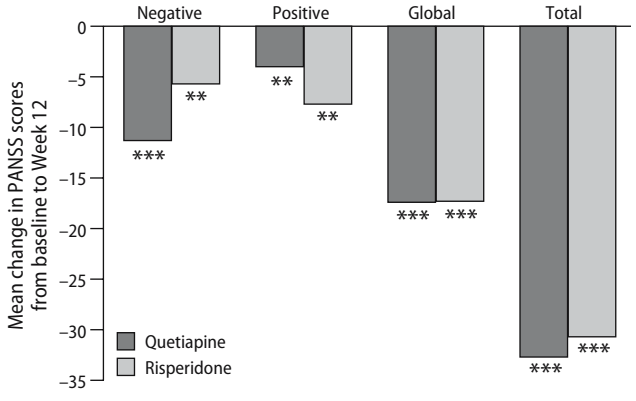


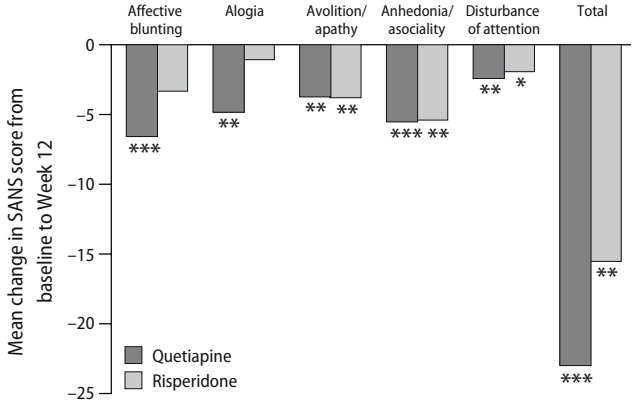
Fig. 2 Mean z-scores for the six cognition domains at baseline, Week 6 and Week 12 following (**a**) quetiapine treatment and (**b**) risperidone treatment

*p < 0.05; **p < 0.01; ***p < 0.001 vs. baseline;‡p < 0.05 vs. risperidone



**p< 0.01; ***p < 0.001 vs. baseline

Fig. 3 Mean change in PANSS total and subscale scores from baseline to Week 12



*p < 0.05; **p < 0.01; ***p < 0.001 vs baseline

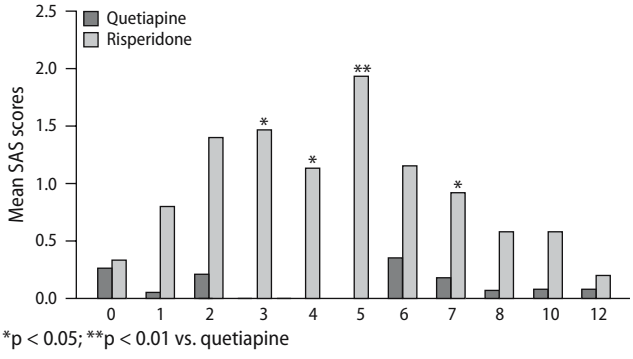
Fig. 4 Mean change in SANS total and attention subscale scores from baseline to Week 12

receiving risperidone, however, this may be associated with the relatively high mean dose of risperidone used during this trial. Seven patients in the risperidone group required anticholinergic medication (biperiden hydrochloride) for EPS occurring during this study, whereas two patients receiving quetiapine required anticholinergic medication from the beginning

Table 5 Number of patients spontaneously reporting adverse events[a]

Adverse event	Quetiapine N (%)	Risperidone N (%)	p
Akathisia	0	5 (33.3)	<0.001
Insomnia	6 (31.6)	3 (20.0)	ns
Dizziness	6 (31.6)	6 (40.0)	ns
Nausea	3 (15.8)	2 (13.3)	ns
Headache	6 (31.6)	5 (33.3)	ns
Tiredness	16 (84.2)	4 (26.6)	<0.001
Parkinsonism	0	6 (40.0)	<0.001
EPS, total	0	9 (60.0)	<0.001

[a] Adverse events occurring in ≥5% of patients in any treatment group
p = between treatment comparison (Fisher's exact test); ns = not significant



*p < 0.05; **p < 0.01 vs. quetiapine

Fig. 5 Mean SAS scores throughout the study

of the study to treat continuing EPS resulting from previous haloperidol therapy. The mean (SD) dose of anticholinergic medication required was significantly higher among those patients treated with risperidone than those receiving quetiapine: 0.94 (1.36) mg/day and 0.03 (0.11) mg/day, respectively ($p \leq 0.01$). At Week 12 other clinical parameters, such as ECG and body weight were not significantly different between treatments.

Discussion

Patients with schizophrenia who have predominantly negative symptoms, as shown by higher PANSS

scores, may have poorer outcomes than those with pronounced positive symptoms [32], particularly when these negative symptoms are accompanied by marked cognitive impairment.

The effects of treatment with the atypical antipsychotics quetiapine and risperidone on cognition have been investigated here in patients with schizophrenia who have predominantly negative symptoms.

Risperidone and quetiapine were effective in the treatment of both negative and positive symptoms of schizophrenia in this study, consistent with results from previous studies [9, 52, 55, 57]. In particular, both treatments improved negative symptoms, measured on the PANSS and SANS. This effect was more marked with quetiapine despite this treatment group having higher baseline scores than patients receiving risperidone.

Significant improvements in various cognitive subdomains were observed during the 12-week study period. The improvements in working memory and verbal memory at Week 6 as well as the improvement in reaction quality/attention at Week 12 in patients following quetiapine treatment were of greater statistical significance than the changes relative to baseline observed at the same timepoints following risperidone treatment, although baseline MWT-B scores were higher in patients receiving risperidone. Change from baseline to Week 12 for both reaction time and visual memory was more pronounced in the risperidone group than in patients taking quetiapine, however, reaction quality/attention decreased.

Working and verbal memory are important predictors of long-term community functioning and rehabilitation potential [69]. Working memory includes the maintenance of information 'online' for ready access [21] and has been found predictive of subjective satisfaction with social relations [13]. Verbal working memory has been closely linked with acquisition of new skills in psychosocial rehabilitation programmes [19] and therefore is a neurocognitive domain of great importance, especially with respect to long-term outcomes. The difference between quetiapine and risperidone in these domains is in contrast to results from a previous study describing the effects of risperidone on working memory [21], where improvement in verbal working memory was found to be greater following treatment with risperidone compared with haloperidol, suggesting that the verbal working memory response to risperidone in the present study would be similar to the response observed with quetiapine.

The neurocognitive domain reaction quality/attention was measured using general attention and vigilance as well as sensomotoric items included in the neuropsychologic diagnostic programme TEST-BAT developed by Wiebel et al. [75]. In the study of Velligan et al. results in this cognitive domain correlated especially with long-term social skills of the patients [69].

In the current study, reaction time improved significantly from baseline in the patients receiving risperidone but not in patients receiving quetiapine. Improvements in reaction time might be linked to improvements in overall outcome [17], which may indirectly improve other related cognitive subdomains.

Treatment with both quetiapine and risperidone improved executive function. Executive function is an important predictor for long-term outcome and is closely associated with community integration and the ability to perform daily activities. Moreover, this subdomain has also been linked with objective measures of financial adequacy, maintenance of family contacts and vocational success [13].

Overall, the differences in the cognitive subdomain scores are consistent with emerging evidence that atypicals have subtle, yet measurably different effects on cognition [6], which might be a result of the different central nervous system receptor-binding profiles of these agents. For example, risperidone and quetiapine both exhibit a low affinity for muscarinic receptors, which may increase cholinergic transmission in the prefrontal cortex and subsequently lead to a positive effect on cognitive symptoms [33, 53]. As a result of its high affinity for dopamine D_2 receptors, risperidone-treated patients showed a higher incidence of EPS and consequently received significantly more anticholinergic medication than patients in the quetiapine group. Use of anticholinergic medication leads to a demonstrable adverse effect on cognitive functions and could have contributed, as a secondary treatment effect, to worsen the performance of risperidone-treated patients in neuropsychological tests [14, 65].

Additional to the blockade of mesolimbic dopaminergic receptors, antagonism of serotonergic 5-HT_{2A} receptors seems to be relevant for improving neurocognitive dysfunction. The blockade of serotonergic receptors leads to increased dopaminergic activity in the prefrontal cortex and to improved transmission at dopamine D_1 receptors in the neocortex [37, 59]. An alternative explanation, the loose-binding concept, has been described by Kapur and Seeman who hypothesised that not only would a combination of a strong 5-HT_{2A} and D_2 receptor blockade be responsible for the 'atypical' effect of the newer antipsychotics, but also the characteristic of a lower affinity to the D_2 receptor combined with a faster dissociation from the receptor, as is the case for some agents, especially quetiapine [35, 36].

In addition, these findings may have important implications for treatment considerations, although further confirmation of these results is required. It may be that specific patterns of neurocognitive impairment could be more successfully treated with a particular atypical antipsychotic. This may lead to a more individualised approach to treatment [61] by allowing the agent most suitable for treating a patient's particular neurocognitive deficits to be used.

There are several limitations to our study; the sample size was comparatively small and consisted of a relatively homogeneous patient population with predominantly negative symptoms and low-grade positive symptoms before study inclusion. However, these negative symptoms were considered primary in nature, and not a secondary consequence of EPS, given the low SAS scores at baseline.

Indeed, patients in the risperidone group were by chance significantly older and had a significantly higher age of onset than patients treated with quetiapine, but on the other hand both groups exhibit a similar duration of illness excluding a more chronic course of the disease in the older risperidone group. However, patients treated with risperidone had a higher MWT-B score at baseline, which is assumed to be correlated with aspects of "crystallised intelligence" and could indicate a higher functional level of these patients. By reason of these aspects it seems to be very unlikely that the higher age of the risperidone patients was responsible for the findings of a minor efficacy of risperidone in some cognitive domains compared to quetiapine.

Besides, patients in the quetiapine group had a higher mean PANSS baseline negative score leading to a higher probability of symptom reduction. The statistical power in the risperidone group was smaller due to a smaller number of patients included. The consequence is that significant findings of within-group testing were less likely, so that the higher amount of within-group differences in the quetiapine group should not be interpreted as a clear superiority. Concerning between-group differences an increased alpha-error cannot be excluded due to multiple statistical tests without correction in order to identify tendential significant correlations. Although we tried to minimise the effect of a priori drug-group differences by using the relevant baseline scores as covariates in the variance analysis the nature of the study has to be considered rather hypothesis-generating than confirmatory.

We have reviewed the influence of cognitive functioning on long-term outcomes for patients with schizophrenia with predominantly negative symptoms of the disease. The results from this 12-week study underline the value of treatments that improve the negative symptoms of schizophrenia thereby enhancing cognitive abilities. In particular, we have described the effects of both quetiapine and risperidone on cognition and observed that changes in cognitive functioning were generally comparable, but with key differences in improvements in certain cognitive domains, depending on the antipsychotic received. For example, greater improvement was seen with quetiapine compared to risperidone in relation to working memory, an important predictor of community functioning and social relations. These results suggest that quetiapine and risperidone provide valuable treatment options for patients with schizophrenia with predominantly negative symptoms. In addition, the improvements in cognition following treatment with quetiapine and risperidone may enhance long-term outcomes for these patients.

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