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ORIGINAL PAPER

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Quetiapine has equivalent efficacy and superior tolerability to risperidone in the treatment of schizophrenia with predominantly negative symptoms

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Abstract Atypical antipsychotics are generally thought to be more effective than conventional agents in treating the negative symptoms of schizophrenia; however, there have been few direct comparisons among atypicals. We therefore investigated risperidone and quetiapine with respect to their efficacy against negative symptoms in a 12-week, double-blind, comparative pilot study involving 44 patients with schizophrenia with predominantly negative symptoms, as defined by Positive and Negative Syndrome Scale (PANSS) scores. Other efficacy measures included the Scale for the Assessment of Negative Symptoms (SANS) and the Clinical Global Impression (CGI) rating scale. Antipsychotic tolerability was assessed using the Simpson-Angus Scale (SAS) and various laboratory measures. Mean doses were 589.7 mg/day quetiapine and 4.9 mg/day risperidone (observed cases). Both antipsychotics produced significant decreases in PANSS total, positive and negative scores, and SANS scores. Patients receiving risperidone were significantly more likely to experience extrapyramidal symptoms (EPS) [$p < 0.05$], or to require anticholinergic medication ($p < 0.05$), and had significantly higher prolactin levels ($p < 0.001$) than quetiapine-treated patients. In conclusion, there is no significant difference in efficacy between quetiapine and risperidone in alleviating the negative symptoms of schizophrenia. Quetiapine is also well tolerated, with a lower incidence of EPS and prolactin increase than risperidone.

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Introduction

Schizophrenia ranks among the most debilitating chronic illnesses, affecting approximately 1 % of the world population (Buchanan and Carpenter 2000) and imposing a huge psychological burden on affected individuals, their dependants and caregivers (Bunney and Meltzer 1995).

There is growing interest in the potential for treating negative symptoms of schizophrenia. Negative symptoms such as affective flattening, poverty of speech, apathy, avolition, anhedonia, asociality and attentional impairment can significantly affect patient function. Patients with predominantly negative symptoms on admission to hospital often have poorer outcomes than those with predominantly positive symptoms.

Although negative symptoms respond, at least partially, to conventional antipsychotics (Meltzer 1990; Tandon et al. 1990), these agents are not considered as effective as the newer atypical antipsychotics. Furthermore, conventional antipsychotics are associated with severe side effects, which may exacerbate secondary negative symptoms (King 1998). Several atypical antipsychotics are currently available, including amisulpride, aripiprazole, quetiapine, olanzapine, risperidone, zotepine and ziprasidone. These agents are believed to be more effective than conventional antipsychotics in treating negative symptoms (Möller 1999b, 1999a), due to better tolerability and a broader neurotransmitter action.

The favourable side-effect profiles of atypical antipsychotics compared with conventional antipsychotics represent a key feature in schizophrenia care. Patients often require long-term treatment and significant side effects contribute to patient nonadherence to medication (Fenton et al. 1997). Problems associated with specific atypicals include substantial weight gain (clozapine, olanzapine) (Allison et al. 1999), prolactin eleva-

tion (risperidone, amisulpride) (Cheer and Wagstaff 2004; Hamner 2002), extrapyramidal symptoms (EPS) [risperidone, olanzapine, ziprasidone, aripiprazole] (Eli Lilly and Company 2003; Daniel et al. 1999; Keck Jr. et al. 2003; Owens 1994), blood dyscrasias [clozapine] (Alvir et al. 1993) and cardiovascular abnormalities (ziprasidone) (Guthrie 2002). Somnolence is also associated with all atypical antipsychotics to varying extents. Olanzapine and clozapine produce dose related somnolence (Conley and Meltzer 2000; Daniel et al. 1996), whereas somnolence associated with quetiapine is not dose related and tends to occur early in treatment and be transient (Goldstein et al. 2005).

Despite growing evidence for the efficacy of atypical antipsychotics against negative symptoms, there is a paucity of direct efficacy comparisons among the atypicals (Leucht et al. 1999). In this pilot study we compare the efficacy and tolerability of the atypical antipsychotics risperidone and quetiapine in patients presenting with mainly negative symptomatology. Based on a previous review of atypical and conventional antipsychotics (Leucht et al. 1999), we hypothesise that significant differences exist between risperidone and quetiapine in alleviating negative symptoms in these patients.

Methods

Design

This randomised, parallel, double-blind trial of 12 weeks duration compared the efficacy and safety of quetiapine and risperidone in patients with schizophrenia presenting with predominantly negative symptoms. Outpatients, partially hospitalised or intermediately hospitalised patients were eligible to participate in the study. All patients gave their written informed consent according to procedures approved by the ethics committee of the University of Munich medical faculty prior to study inclusion.

Upon entering the study, a thorough medical and psychiatric history, complemented by chart review, if available, was carried out. Additionally, each patient received a medical check-up including physical examination, electrocardiogram (ECG), electroencephalogram (EEG), laboratory tests, urine drug screen and pregnancy test, if applicable. The same check-up procedure was performed on all patients at endpoint or after withdrawal, whichever occurred first.

Each patient underwent a washout period of 2 days before the beginning of the trial to ensure dopamine receptor occupancy levels returned to baseline values. This short washout period was in adherence to ethical guidelines and was chosen to reduce the probability of illness deterioration.

Patients

Patients were recruited into the study if they met DSM-IV (American Psychiatric Association, 1996) and ICD-10 criteria for schizophrenia, had a Clinical Global Impression (CGI) score ≥ 4 (Guy 1976), and presented with predominantly primary negative symptoms according to the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987), with a PANSS negative subscale score ≥ 21 and at least 1 point greater than their positive subscale score. Exclusion criteria included drug or alcohol abuse/dependence, suicidal tendencies, laboratory or ECG/EEG abnormalities (blood or urine values outside standard range by more than 20 %), pregnancy or lactation, significant medical history (brain surgery, unstable somatic conditions, HIV +), and treatment with clozapine within 4 weeks of enrolment.

Treatment

At the start of the study, patients were randomly assigned to receive quetiapine or risperidone. Quetiapine was initiated as follows: 50 mg on day 1, 100 mg on day 2, and then daily 100 mg increments to 600 mg/day on day 7. 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, the dose of study medication was adjusted according to the clinical judgement of the investigators. The maximum doses allowed were 800 mg/day quetiapine and 8 mg/day risperidone, respectively. If a patient did not sufficiently respond to the maximum doses, the treatment was terminated and other appropriate treatment was arranged. Both risperidone and quetiapine were packed by the hospital's pharmacy in lactose capsules containing 100 mg quetiapine or 1 mg risperidone, with identical size and appearance to maintain treatment blindness throughout the trial. Lorazepam (≤ 4 mg/day) and zopiclone (≤ 15 mg/day) were allowed throughout the trial for agitation and insomnia. Biperiden hydrochloride (≤ 8 mg/day) was used to treat EPS. Besides standard clinical management, no additional psychotherapy was performed.

Efficacy and tolerability assessments

Efficacy and tolerability assessments were carried out on a regular weekly basis. All assessments were performed by trained medical personnel and included monitoring of vital signs, laboratory check-ups and psychopathological as well as side-effect evaluation. Adherence was assessed by weekly pill counts. In addition, body weight measurements, and ECG to monitor cardiac safety, were obtained at weeks 2, 6, 10 and 12.

Treatment efficacy was assessed using a number of standardised rating scales. The primary measure of psychopathology used was the PANSS. The Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1989) was employed to further evaluate negative symptoms. Overall treatment response was assessed using the CGI scale.

EPS were assessed using the Simpson-Angus Scale (SAS) (Simpson and Angus 1970). Regular ECGs, weekly laboratory assessments (haematology, chemistry, thyroid, urinalysis) and measurement of vital signs were also included in the safety assessment. Furthermore, adverse events were recorded as additional indicators of tolerability and safety during the trial.

Statistical methods

The primary endpoint for efficacy and safety was week 12. The analyses encompassed all patients randomised with baseline data and at least one post-baseline measure (i. e. intent-to-treat subjects). Evaluation of efficacy was based on a last observation carried forward (LOCF) approach used to substitute for missing values in efficacy variables. The primary outcome variable was change in PANSS negative subscale score. Intent-to-treat analyses of efficacy were corroborated by completer analyses (i. e. analysis of data only from patients who completed the trial). In either case, analyses were based on two-sided paired t-tests to compare the means (baseline vs. endpoint) for each treatment group. Efficacy and tolerability of risperidone and quetiapine were compared by two-sample t-tests. As age at illness onset and age at study entry were significantly different between the treatment groups, t-tests were supplemented by analyses of covariance models (ANCOVA) including these two variables as covariates. To account for a potential imbalance in baseline scores between the treatment groups, the baseline measurement of the variable investigated was included as an additional covariate in ANCOVA models. Significant findings were only reported if they were consistently replicated using all of the methods applied.

Frequencies of dichotomous variables (e. g. of adverse events) were compared using Chi-square statistics including Yates' continuity correction when $n > 5$ and Fisher's exact test when $n < 5$. P values ≤ 0.05 (two-sided) were considered statistically significant.

Results

Patients

Forty-four patients (27 males and 17 females) with pronounced negative symptomatology were recruited into the study (no patients were excluded after screening). An equal number of patients ($n = 22$ per group) were randomised to each of the study groups. Dropout rates were 41 % with quetiapine (adverse events 0, lack of efficacy 3, consent withdrawn 4, lost to follow-up 2) and 45 % with risperidone (adverse events 3, lack of efficacy 5, consent withdrawn 2, lost to follow-up 0). The three risperidone patients who withdrew due to adverse events did so as a result of both akathisia and parkinsonism. Thirteen patients in the quetiapine group and 12 in the risperidone group completed the 12-week study. A summary of proband flow is shown in Table 1.

Baseline clinical data of the study sample are shown in Table 2. There were higher PANSS negative, SANS alogia, SANS avolition-apathy and SANS total scores at baseline in the quetiapine-treated group compared with the risperidone group. Age at illness onset and age at study entry were found to be higher with risperidone as compared with quetiapine. All other variables investigated were found to be similar in the two treatment groups (Table 2).

Treatment

The mean doses of medication in the quetiapine and risperidone groups were 589.7 mg/day and 4.9 mg/day, respectively. Mean treatment duration was 66.1 days in the quetiapine group and 62.7 days in the risperidone group.

Table 1 Proband flow

Quetiapine			Risperidone		
Randomised n = 22			Randomised n = 22		
Withdrawals n = 9			Withdrawals n = 10		
Sex	Day of withdrawal	Reason for withdrawal	Sex	Day of withdrawal	Reason for withdrawal
M	5	4	F	7	2
M	8	2	M	14	2
F	21	4	F	28	2
M	35	2	M	28	4
M	42	4	M	35	1
F	56	2	M	35	1
F	56	3	F	42	1
F	70	3	F	56	4
F	70	4	M	70	2
			M	77	2
Completers n = 13			Completers n = 12		

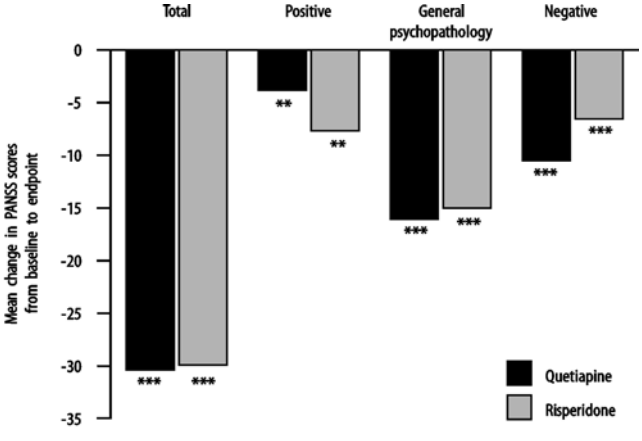
Sex: *M* Male; *F* Female
All 44 patients screened were randomised
Reason for withdrawal: 1 = adverse events, 2 = lack of efficacy, 3 = lost to follow-up, 4 = consent withdrawn

Table 2 Baseline clinical characteristics and demographics

	Quetiapine (n = 22)	Risperidone (n = 22)
Male/Female	15/7	12/10
Mean age, years	30.6 ± 10.9	39.3 ± 12.3
Body weight, kg	74.9 ± 15.4	75.5 ± 13.4
Age of onset, years	25.3 ± 10.5	36.9 ± 17.7
Duration of illness, years	5.4 ± 7.5	2.5 ± 12.7
PANSS total	103.4 ± 16.4	97.8 ± 16.9
PANSS positive	19.1 ± 6.6	21.7 ± 7.3
PANSS negative	31.0 ± 5.9	25.7 ± 7.0
PANSS global	53.3 ± 9.7	50.3 ± 10.4
SANS total	66.7 ± 20.6	51.7 ± 21.1
SANS affective blunting	18.6 ± 7.4	13.7 ± 8.6
SANS alogia	13.2 ± 5.9	8.9 ± 6.1
SANS avolition-apathy	12.1 ± 3.4	9.7 ± 3.6
SANS anhedonia asociality	15.3 ± 3.9	13.3 ± 4.6
SANS attention	7.6 ± 3.1	6.1 ± 3.2
SAS score	0.2 ± 1.1	0.5 ± 1.3

Efficacy

Treatment with both risperidone and quetiapine significantly improved overall symptoms at week 12, as depicted by mean changes in PANSS total, and PANSS positive, negative, and general psychopathology subscale scores ($p < 0.01$) (Fig. 1), compared with baseline. These results were confirmed by completer analyses ($p \leq 0.01$ in both treatment groups for the PANSS total score and for all PANSS subscale scores). Both quetiapine and risperidone significantly reduced negative symptoms as early as week 1 and this improvement continued up to week 12 ($p \leq 0.01$ vs. baseline at all timepoints for both



**p < 0.01; ***p < 0.001 vs. baseline (paired t-tests)

Fig. 1 Mean change in PANSS total and subscale scores from baseline to week 12 following treatment with quetiapine or risperidone

agents). By week 12, the PANSS negative subscale score for quetiapine had decreased by –12.8 from a baseline of 31.0; risperidone had decreased by –4.2 from a baseline of 25.7. No statistically significant differences between the quetiapine and risperidone groups were found in the PANSS subscales over the trial duration.

Treatment with quetiapine resulted in significant improvements versus baseline in SANS total ($p < 0.001$), affective blunting ($p < 0.001$), alogia ($p < 0.001$), avolition ($p < 0.001$), anhedonia ($p < 0.001$), and disturbance of attention ($p < 0.01$) scores (Fig. 2). By comparison, treatment with risperidone only resulted in significant improvements in SANS total ($p < 0.01$), avolition ($p < 0.01$), anhedonia ($p < 0.01$), and disturbance of attention ($p < 0.01$) scores. These results were confirmed by completer analyses. With quetiapine, the SANS total score and all SANS subscale scores significantly improved from baseline to week 12 ($p < 0.001$ for all items except 'disturbance of attention', $p < 0.01$). With risperidone, completer analyses only showed significant improvements in SANS total ($p < 0.01$), avolition ($p < 0.01$), anhedonia ($p < 0.01$), disturbance of attention ($p < 0.02$) and affective blunting ($p < 0.01$) scores. The change in the SANS alogia item between the two groups showed a tendency towards a significant advantage for quetiapine over risperidone in simple comparison of means ($t = 1.899$, $df = 42$, $p = 0.065$) but not when age, age at onset, and the SANS alogia baseline score were included as covariates ($f = 1.805$, $df = 1.39$, $p = 0.187$). Besides alogia, a numerically greater decrease in SANS subscale scores with quetiapine treatment was observed in affective blunting, anhedonia and disturbance of attention, although this was not statistically significant.

Overall, patients were similarly rated by clinicians regarding their overall improvement. Both treatment groups showed marked improvement, as reflected by mean changes of CGI scores at week 12 (mean-change: quetiapine = 1.7 ± 1.4, risperidone = 1.5 ± 1.6; $p = 0.767$).

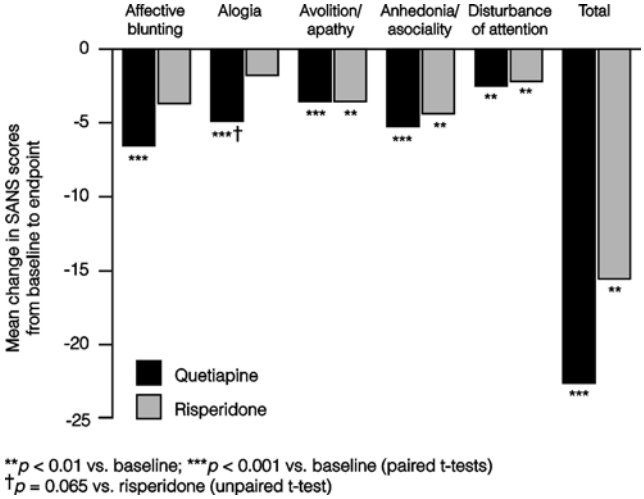


Fig. 2 Mean change in SANS scores from baseline to week 12 following treatment with quetiapine or risperidone

Tolerability

Results from ECGs and EEGs were not significantly different between the two treatment groups. The most frequent adverse events (i. e. with an incidence of > 10 %) are summarised in Table 3. Patients receiving quetiapine had a higher incidence of tiredness ($p < 0.001$) although this was mild to moderate in intensity and was transient in the majority of patients (< 2 weeks duration in 88 % of patients who experienced somnolence). Patients treated with risperidone had a significantly higher incidence of akathisia and parkinsonism ($p = 0.006$). Furthermore, at weeks 3, 4, 5 and 7, risperidone-treated patients had significantly greater SAS scores (1.81, 2.11, 2.53 and 0.8) compared with quetiapine-treated patients (0, 0, 0 and 0.17) (p < 0,05 at weeks 3, 4 and 7, p < 0, 01 at week 5), indicating an increased incidence and severity of EPS in the risperidone group.

A significantly greater number of patients in the risperidone group required anticholinergic medication (biperiden hydrochloride) compared with the quetiapine group ($n = 9$ vs 2, $p = 0.037$). Patients in the quetiapine group received anticholinergic medication from the beginning of the study to treat continuing EPS resulting from haloperidol therapy. Patients in the risperidone group required anticholinergic medication to treat EPS occurring during the study as a result of risperidone therapy. In addition, biperiden-treated patients in the risperidone group required higher mean doses of biperiden hydrochloride (2.57 ± 1.13 mg/day) than biperiden-treated patients in the quetiapine group (0.36 ± 0.0 mg/day). There were no differences in the usage of lorazepam or zopiclone between the treatment groups.

There was no statistically significant difference in the amount of weight gained by patients in each treatment group (risperidone + 1.72 ± 3.57 kg; quetiapine 2.93 ± 4.02 kg, $p = 0.296$). Only one risperidone patient and three quetiapine patients increased in weight by > 7 %.

Treatment with quetiapine resulted in a significant decrease in serum prolactin levels at week 6 ($p < 0.05$) (n = 18) compared with baseline. In contrast, risperidone treatment resulted in a significant increase in serum prolactin levels ($p = 0.001$) (n = 16). The differ-

Table 3 Adverse events occurring in > 10 % of patients

Adverse events	Quetiapine n (%) (n = 22)	Risperidone n (%) (n = 22)	p (Chi-squared)
Akathisia	0	8 (36.4)	0.006
Cold	3 (13.6)	4 (18.2)	0.680
Headache	6 (27.3)	7 (31.8)	0.741
Tiredness	17 (77.3)	5 (22.7)	< 0.001
Parkinsonism	0	8 (36.4)	0.006
Insomnia	6 (27.3)	5 (22.7)	0.728
Dizziness	6 (27.3)	6 (27.3)	1.000
Nausea	4 (18.2)	2 (9.1)	0.660

ence between the two treatments was statistically significant ($p < 0.001$) (Fig. 3). Cortisol levels decreased slightly with both quetiapine ($p = 0.44$) and risperidone ($p = 0.83$). Levels of oestrogen increased slightly with quetiapine treatment ($p = 0.059$) and decreased with risperidone ($p = 0.072$), the difference between treatments was statistically significant ($p < 0.01$) (Fig. 3). Compared with quetiapine, risperidone induced a significant decrease in levels of testosterone and sex hormone-binding globulin ($p < 0.05$) (Fig. 3). Serum hormone levels at week 12 are not shown due to low patient numbers ($n = 10$).

Discussion

In order to accurately assess the efficacy of antipsychotic agents against the negative symptoms of schizophrenia, it is important to study a patient population with predominantly negative symptoms. In the present study, our treatment groups constituted a fairly homogeneous patient sample with predominant negative symptomatology; positive symptoms were low on admission. Also, EPS, which might contribute to the phenomenology of negative symptoms, were low on admission and remained so throughout the trial. Therefore, negative symptoms in this study sample may be considered primary in nature.

In the present study, significant improvements in negative symptomatology occurred as early as week 1 with both quetiapine and risperidone. This agrees with a recent study reporting clinical efficacy with quetiapine within the first week of treatment (Small et al. 2004; Zhong et al. 2003). We found quetiapine and risperidone to be similarly efficacious in all clinical measures over the 12-week period, with no significant difference in PANSS total scores, PANSS positive and negative subscores, CGI scores and SANS scores.

The tolerability profile of quetiapine was advantageous compared with risperidone, as evidenced by the level of withdrawals due to adverse events in each treatment group. Also, major differences were found in their propensities to cause EPS. Quetiapine-treated patients were significantly less likely to experience EPS, or to require anticholinergic medication, compared with risperidone-treated patients. Patients receiving risperidone also required higher mean doses of anticholinergic medication than patients in the quetiapine group, indicating a greater severity of EPS experienced by risperidone patients. Previous reports have shown that risperidone is associated with dose-related increases in EPS (Owens 1994). By contrast, quetiapine has been shown to have a placebo-like incidence of EPS (including akathisia) across its full dose range (Arvanitis et al. 1997). As EPS are recognised as a major contributor to secondary, treatment-related negative symptoms, treatment with quetiapine is likely to lead to better functioning and quality of life.

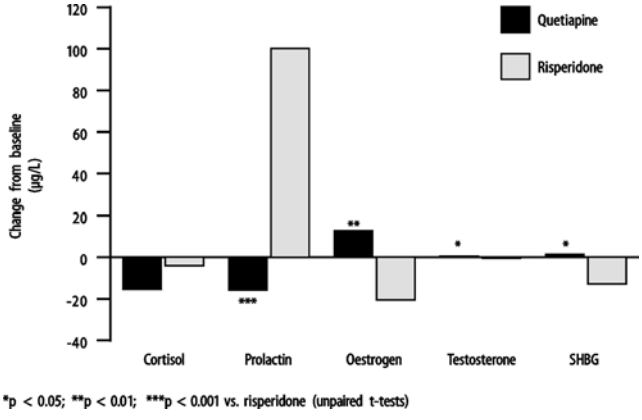


Fig. 3 Mean change from baseline in serum hormone levels at week 6 following treatment with quetiapine or risperidone (*SHBG* sex hormone-binding globulin)

Quetiapine was also significantly less likely to cause hyperprolactinaemia compared with risperidone. This agrees with previous studies in which quetiapine was shown to result in a normalisation of prolactin levels when patients were switched to quetiapine from a previous antipsychotic therapy (Emsley et al. 2000; Meats 1997). In this regard, quetiapine can be a valuable therapeutic option when seeking to minimise sexual adverse events, which can impact upon quality of life (Compton and Miller 2002).

The small sample size (13/22 quetiapine patients and 12/22 risperidone patients at study endpoint) may be regarded as a limitation of this study; however, significant findings were reported only if they were consistently replicated by both LOCF and completer analyses. The results of this pilot study indicate that both quetiapine and risperidone have similar efficacy in alleviating the negative symptoms of schizophrenia, as reflected by similar decreases in PANSS and SANS total and subscale scores. The results of this study also indicate that risperidone and quetiapine are both valuable therapeutic options for the long-term treatment of the negative symptoms of schizophrenia as both were well tolerated, though quetiapine did exhibit a definite advantage in terms of EPS, particularly parkinsonism and akathisia, and serum prolactin levels. Further studies are warranted to confirm these findings.

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