Comparison of Quetiapine and Risperidone in the Treatment of Schizophrenia: A Randomized, Double-Blind, Flexible-Dose, 8-Week Study

Kate X. Zhong, M.D.; Dennis E. Sweitzer, Ph.D.; Robert M. Hamer, Ph.D.; and Jeffrey A. Lieberman, M.D.

Objective: To compare the efficacy and tolerability of quetiapine and risperidone in the treatment of schizophrenia.

Method: In this 8-week, double-blind, multicenter, flexible-dose study, patients with schizophrenia (DSM-IV diagnosis) were randomly assigned to quetiapine (200–800 mg/day) or risperidone (2–8 mg/day). The primary hypothesis was that quetiapine was not inferior to risperidone. The primary efficacy measure was change from baseline in Positive and Negative Syndrome Scale (PANSS) total scores; secondary outcomes included response rate (≥ 40% reduction in PANSS scores), Clinical Global Impression-Change (CGI-C), and cognitive and social functioning. Tolerability assessments included treatment-emergent adverse events and changes in weight, glucose, and prolactin. Patients were recruited from June 2001 to September 2002.

Results: Patients (N = 673) were randomly assigned to quetiapine (N = 338, mean dose = 525 mg/day) or risperidone (N = 335, mean dose = 5.2 mg/day). The primary analysis demonstrated noninferiority between treatments ($p < .05$). Improvements with both treatments were comparable on PANSS total, negative, and general psychopathology subscales. Risperidone-treated patients had a significantly ($p = .03$) greater improvement in PANSS positive subscale score among all patients, but not among completers. Improvements in PANSS response rates, CGI-C, and cognitive function were similar between treatment groups. Changes in serum glucose and weight were minimal and comparable. The rate of extrapyramidal symptom (EPS)–related adverse events was significantly higher with risperidone (22%) than quetiapine (13%; $p < .01$). Somnolence was more common with quetiapine (26%) than risperidone (20%; $p = .04$). Prolactin levels increased with risperidone (+35.5 ng/mL), but decreased with quetiapine (–11.5 ng/mL; $p < .001$).

Conclusions: Quetiapine and risperidone had broadly comparable clinical efficacy. Both agents improved cognitive and social functioning, and neither had a clinically significant effect on weight or glucose. Somnolence was more common with quetiapine; EPS and elevated prolactin rates were significantly higher with risperidone.

(J Clin Psychiatry 2006;67:1093–1103)

Received Aug. 22, 2005, accepted May 16, 2006. From AstraZeneca Pharmaceuticals LP, Wilmington, Del. (Drs. Zhong and Sweitzer); the Department of Psychiatry, University of North Carolina, Chapel Hill, N.C. (Dr. Hamer); and the Department of Psychiatry, Columbia University, New York, N.Y. (Dr. Lieberman). Dr. Zhong is a former employee of AstraZeneca.

The study was funded by AstraZeneca. Drs. Lieberman and Hamer participated in supervision and interpretation of data analyses and in the drafting and revision of the manuscript. Sally K. Laden, M.S., provided medical writing support on behalf of AstraZeneca.

Financial disclosure appears at the end of this article.

Participating investigators are listed at the end of this article.

Corresponding author and reprints: Dennis E. Sweitzer, Ph.D., AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19850 (e-mail: Dennis.sweitzer@astrazeneca.com).

Schizophrenia is a complex, multifaceted illness characterized by 4 groups of symptoms: positive, negative, cognitive, and affective. As such, schizophrenia is a distressing and disabling disorder for the patient and poses a significant burden to these individuals, their families, and society. Conventional antipsychotic medications ameliorate the symptoms of schizophrenia and have been the cornerstone of treatment for nearly 40 years.[1] However, the risks associated with some of these agents, including extrapyramidal symptoms (EPS) and tardive dyskinesia, limit and may outweigh any therapeutic benefits. In the early 1990s, clozapine was introduced in the United States as the first of a new generation of atypical antipsychotics and was found to be more effective than the older agents in treating the positive and negative symptoms of schizophrenia. The subsequent development of other atypical antipsychotics without the adverse event profile of clozapine led to their broad acceptance as a first-line treatment for schizophrenia.[1–4]

Decisions about which atypical antipsychotic to select for individual patients are complex.[4] Comparative studies of atypical antipsychotics are valuable to clinicians who must tailor treatment for individual patients. Risperidone and quetiapine, 2 commonly used atypical antipsychotic medications, have been shown to be efficacious in treating patients with schizophrenia.[5–14] However, the majority of data with these agents come from registration trials that compared the atypical antipsychotics with placebo, and there are only limited trial data on the relative efficacy of risperidone and quetiapine. In fact, the scarcity of

  © Copyright 2006 Physicians Postgraduate Press, Inc.

controlled trial data on the comparative efficacy and safety of the atypical antipsychotics represents a significant gap in our clinical knowledge base. In a large, open-label trial, 728 patients with schizophrenia or other psychotic disorders were treated with either risperidone or quetiapine for 16 weeks.[12] Similar improvements in the Positive and Negative Syndrome Scale (PANSS) total scores were seen in patients in both treatment groups. The similar efficacy of risperidone and quetiapine was subsequently reported from 2 comparative studies.[15,16] However, the small sample size of these studies precludes a definitive comparison of efficacy and tolerability.

In this report, we present the results of an 8-week, randomized, double-blind study comparing the efficacy and tolerability of quetiapine and risperidone in the treatment of patients with schizophrenia. The effects of both agents on cognition and social functioning will also be discussed briefly.

METHOD

Study Design

This trial was an 8-week, multicenter, double-blind, randomized, flexible-dose comparison of quetiapine and risperidone in the treatment of schizophrenia, study number 5077US/0043. Patients from 66 centers in the United States were recruited between June 2001 and September 2002. Participants underwent a 1-week screening period, after which eligible patients were randomly assigned to either quetiapine or risperidone for an 8-week treatment period. All patients were hospitalized for a minimum of 7 days following randomization and were treated on an outpatient basis when their condition stabilized.

Inclusion/Exclusion Criteria

Eligible participants fulfilled all of the following inclusion criteria at baseline: 18 to 65 years of age; *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), diagnosis of schizophrenia (catatonic, disorganized, paranoid, or undifferentiated subtypes); total score ≥ 60 on the PANSS[17]; a score of ≥ 4 on 1 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, suspiciousness, or persecution; and a Clinical Global Impression (CGI) Severity of Illness[18] score of ≥ 4, with evidence of clinical deterioration during the 3 weeks preceding randomization. The institutional review board at each center approved the informed consent procedure and study protocol. Study procedures were explained, and written informed consent was witnessed and obtained from all patients or their legal guardians prior to screening.

The exclusion criteria were as follows: DSM-IV Axis I disorder other than schizophrenia (e.g., schizoaffective disorder, major depressive disorder, alcohol or drug dependence); psychotic disorder due to a general medical condition; mental retardation; known intolerance (i.e., if a patient had previously had an allergic reaction to or was unable to tolerate a medication) or lack of response (in the investigator's clinical judgment) to previous treatment with quetiapine or risperidone; use of clozapine within 1 month of randomization; and use of prohibited medications. Pregnancy, lactation, or failure to use reliable contraception were additional exclusion criteria for female patients.

Concomitant Medications

Use of the following medications was prohibited during the trial: antipsychotics, antidepressants, anxiolytics, mood stabilizers, and potent cytochrome P450 inducers (e.g., carbamazepine, phenobarbital) and inhibitors (e.g., ketoconazole, erythromycin). Anticholinergics were permitted only for the treatment of EPS on a p.r.n. basis. Lorazepam was permitted only for agitation up to and not beyond day 3 of the study.

Dosing Regimen

Patients assigned to the quetiapine group received 50 mg of quetiapine on day 1 and 100 mg on day 2, after which the daily dose was titrated in 100-mg increments up to 400 mg per day on day 5. Patients assigned to the risperidone group received 2 mg of risperidone on days 1 and 2, after which the daily dose was increased to 3 mg on days 3 and 4, and then 4 mg on day 5. Starting on day 6, investigators could adjust the doses according to the patient's clinical response and tolerability; quetiapine could be flexibly adjusted from 200 to 800 mg/day, and risperidone could be flexibly adjusted from 2 to 8 mg/day. Study medications were administered orally as identical, encapsulated tablets on a twice-daily basis throughout the 8-week randomized treatment period.

Assessments

Patients were assessed at baseline (day 1) and on days 4, 8, 15, 28, 42, and 56. The primary efficacy measure was change in the PANSS total score from baseline to week 8 or study withdrawal. Secondary efficacy measures included the percentage of patients rated "very much" (score of 1) or "much" (score of 2) improved on the CGI-Change (CGI-C) scale[18]; the proportion of patients achieving ≥ 40% reduction in PANSS total and subscale scores; the proportion of patients who had ≥ 30% reduction in PANSS total and subscale scores; and the change from baseline to final assessment in PANSS positive, negative, and general psychopathology subscale scores.

In addition to the clinical assessments described above, assessments of cognitive performance, social cognition, and social competence were obtained. The cognitive assessments included measures of vigilance (the continuous performance test[19]), processing speed (trail making parts A and B[20]), verbal learning and delayed recall (Rey verbal

Table 1. Demographic and Baseline Characteristics

Characteristic	Quetiapine (N = 338)	Risperidone (N = 335)
Gender, %		
Male	77.1	74.4
Female	22.9	25.6
Race, %		
White	38.4	39.1
African American	50.6	50.9
Hispanic	7.3	7.8
Other	3.6	2.2
Age, mean (SD), y	40.2 (10.8)	39.6 (10.8)
Serum glucose, mean (SD), mg/dL	99.1 (33.2)	100.4 (32.9)
Weight, mean (SD), kg	85.3 (21.7)	87.8 (21.1)
BMI, mean (SD)	28.5 (7.2)	28.8 (6.9)
Serum prolactin, mean (SD), ng/mL	22.7 (29.2)	22.6 (26.7)
PANSS total score, mean (SD)	92.9 (19.7)	92.1 (17.5)
CGI-Severity of Illness score, mean (SD)	4.6 (0.7)	4.6 (0.7)
Previous medications, N (%)	326 (96.4)	319 (95.2)
Olanzapine	122 (36.1)	135 (40.3)
Risperidone	99 (29.3)	92 (27.5)
Haloperidol	55 (16.3)	63 (18.8)
Quetiapine	45 (13.3)	33 (9.9)
Ziprasidone	27 (8.0)	14 (4.2)
Chlorpromazine	8 (2.4)	8 (2.4)
Loxapine	3 (0.9)	4 (1.2)
Clozapine	2 (0.6)	0
Molindone	0	1 (0.3)

Abbreviations: BMI = body mass index, CGI = Clinical Global Impressions, PANSS = Positive and Negative Syndrome Scale.

learning test[21]), and verbal skills (category and phonological fluency[22]). Social function was assessed using the Penn Emotional Acuity Test (PEAT),[23] and social competence was examined with a performance-based measure, the Social Skills Performance Assessment (SSPA).[24]

Spontaneous reports of treatment-emergent adverse events were collected at each visit. Clinical laboratory assessments, including serum prolactin and random serum glucose levels, vital signs, and changes in body weight, were conducted at baseline and at week 8 or study withdrawal. Changes from baseline to final assessment on the Simpson-Angus Scale (SAS),[25] Abnormal Involuntary Movement Scale (AIMS),[26] and Barnes Akathisia Rating Scale (BARS)[27] were used to assess EPS.

Statistical Analysis

The primary hypothesis of this study was that quetiapine was not inferior to risperidone in treating patients with schizophrenia. The primary efficacy measure was change from baseline to final assessment in the PANSS total score. Assumptions for the noninferiority analysis included (1) an equivalence margin of 6 points between treatment arms in the PANSS total score based on a literature review of comparable clinical trials (i.e., differences of < 6 points in the PANSS total score were not considered clinically significant), (2) a statistical significance level of $p = .05$, and (3) a 1-tailed statistical test. Consequently, a statistically significant noninferiority test with $p < .05$ implies that quetiapine is not inferior to risperidone with 95% certainty. The sample size was chosen to ensure 90% power for a statistical test of noninferiority, assuming that (1) there was truly no difference between treatments in the outcome and (2) the standard deviation (SD) of the change from baseline in PANSS total scores was < 25 (as observed in other trials with similar patient populations). Secondary efficacy endpoints were analyzed as superiority tests in order to estimate treatment differences with 95% confidence intervals. All secondary tests were 2-tailed with a statistical significance level of $p = .05$. Consequently, for all secondary endpoints (i.e., from a superiority test), $p < .05$ implies that a statistically significant difference between treatments was found, in contrast to the primary noninferiority test.

All efficacy analyses were performed on the modified intent-to-treat (MITT) population, which consisted of all patients who were randomly assigned to treatment, received at least 1 dose of study medication, and had at least 1 postbaseline assessment. Results are presented for completers and for all patients (last observation carried forward [LOCF]) at week 8 and for observed cases (OC) by visit. Analysis of covariance (ANCOVA) was used to analyze the change from baseline in PANSS total and subscale scores, which included baseline score as a covariate and center as a random effect.

Analyses of safety and tolerability assessments were conducted on the safety population, which consisted of all randomized patients who received at least 1 dose of study medication. ANCOVA was used to analyze the change from baseline on BARS, SAS, and AIMS, and the change from baseline in prolactin levels (including sex as a covariate), body weight, and random serum glucose levels, using the respective baseline values as covariates in each case. The binary outcomes of ≥ 40% reduction in PANSS total and subscale scores and the percentage of patients with a CGI-C rating of < 3 ("much" or "very much" improved) were tested for treatment differences using Cochran-Mantel Haenszel χ^2 tests. Between-group differences in frequent adverse events (occurring in ≥ 5% of patients), categorical incidence of sexual/reproductive adverse events, and EPS-related adverse events were tested using the Fisher exact test.

RESULTS

Patients

A total of 872 patients were screened, and 673 were randomly assigned to either quetiapine (N = 338) or risperidone (N = 335). The patient demographic characteristics and baseline measures were similar between groups (Table 1). The study sample consisted largely of men in their late 30s or early 40s. The proportion of men in the quetiapine group (77.1%) was slightly greater than in the risperidone group (74.4%). Approximately 50% of the pa-

  © Copyright 2006 Physicians Postgraduate Press, Inc.

Table 2. Patient Disposition

Disposition	Quetiapine (N = 338), N (%)	Risperidone (N = 335), N (%)
Completed study	154 (45.6)	168 (50.1)
Discontinued treatment (total)	184 (54.4)	167 (49.9)
Lost to follow-up	25 (7.4)	40 (11.9)
Adverse event	19 (5.6)	25 (7.5)
Protocol deviation	22 (6.5)	19 (5.7)
Withdrew consent	28 (8.3)	34 (10.2)
Lack of efficacy	82 (24.3)	46 (13.7)
Other	8 (2.4)	3 (0.9)

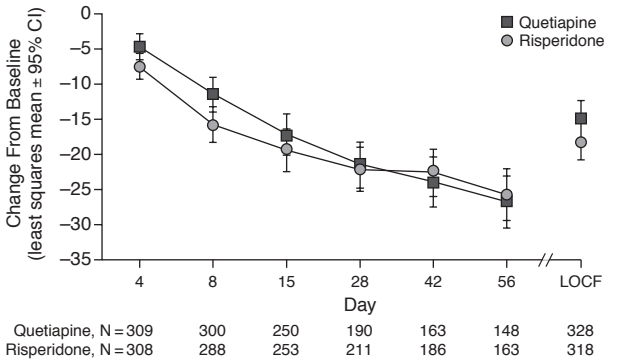
tients in both groups were African American, and a substantial minority was white (39%). This population was moderately to severely ill, with patients in both treatment groups having mean PANSS total scores of > 92 and CGI-Severity of Illness scores of 4.6 at baseline.

Study completion rates were similar for quetiapine and risperidone (45.6% and 50.3%, respectively; p = .2) (Table 2). The proportion of patients withdrawing from the study because of adverse events was higher with risperidone than with quetiapine. The proportion of patients withdrawing due to lack of efficacy was higher with quetiapine than with risperidone. The mean duration of randomized treatment was 34.7 days (SD = 21.3) for patients in the quetiapine group and 36.5 days (SD = 21.9) for patients in the risperidone group. One patient withdrew from the study before receiving the first dose of risperidone, and thus the safety populations for quetiapine and risperidone were 338 and 334 patients, respectively. Ten patients from the quetiapine group and 14 from the risperidone group were excluded from the efficacy analyses because either baseline or first postbaseline PANSS scores were missing. Thus, the MITT populations were 328 patients in the quetiapine group and 320 patients in the risperidone group.

Medication Doses

Doses are reported as the mean of the median doses for individual patients. In the quetiapine group, 44.4% of patients had a median dose of 400 to 600 mg/day, with 21% of patients receiving a lower dose and 34.6% receiving a higher dose. In the risperidone group, 48.5% of patients had a median dose of 4 to 6 mg/day, with 21.9% of patients receiving a lower dose and 29.6% receiving a higher dose. The overall mean median doses were 525 mg/day (SD = 231) for quetiapine-treated patients and 5.2 mg/day (SD = 2.1) for risperidone-treated patients. For patients who completed the study, the mean median doses were 626 mg/day (SD = 174) for quetiapine and 6.0 mg/day (SD = 1.8) for risperidone, while the mean median doses for responders (patients achieving ≥ 40% reduction in PANSS total scores) were 574 mg (SD = 189) for quetiapine and 5.6 mg (SD = 1.9) for risperidone. Among patients who withdrew due to lack of efficacy, the mean doses were 429 mg (SD = 240) and 4.7 mg (SD = 2.3) for quetiapine and risperidone, respectively.

Figure 1. PANSS Total Score: Change From Baseline[a]



[a]No significant difference between groups at either week 8 or endpoint.
Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

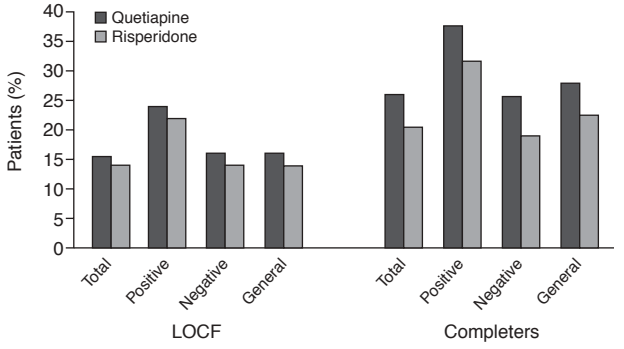
Efficacy

Patients in both treatment groups showed an improvement in PANSS total scores. The noninferiority analysis of the primary efficacy measure demonstrated that quetiapine was not inferior to risperidone among all MITT patients (LOCF; p < .05), among completers (p < .01), or when patients with significant protocol violations or deviations were excluded (p < .02). There were no significant differences between groups in the change from baseline in PANSS total scores for either LOCF or OC analyses at each visit (Figure 1). At the end of treatment (LOCF), PANSS total scores fell by –15.1 (SE = 1.4) in quetiapine-treated patients and –18.1 (SE = 1.4) in risperidone-treated patients. A greater magnitude of improvement was observed among patients who completed the study, for whom the reduction in PANSS total scores from baseline was –27.0 (SE = 1.8) and –25.9 (SE = 1.8) for quetiapine and risperidone, respectively.

Similar proportions of patients in both groups achieved a ≥ 40% reduction in PANSS total and positive, negative, and general psychopathology subscale scores. Between-group differences were not statistically significant for all patients at endpoint (LOCF) or for completers at week 8 (Figure 2). The proportions of patients in the quetiapine and risperidone groups (LOCF) who achieved a ≥ 30% reduction in PANSS total scores were also similar (27.4% and 27.7%, respectively).

Improvements in PANSS subscale scores were achieved by patients in both treatment groups (Table 3). Reductions in the PANSS positive subscale score were significantly greater for risperidone (–5.6, SE = 0.4) than for quetiapine (–4.5, SE = 0.4; p = .03) in the LOCF analysis. In the completer analysis, there was no significant

Figure 2. Response Rate: Proportion of Patients With a ≥ 40% Reduction in PANSS Scores[a]



[a]No significant difference between treatment groups.
Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

difference between risperidone (–8.0, SE = 0.5) and quetiapine (–8.1, SE = 0.5; p = .751). There were no significant differences between treatment groups in the change from baseline in the PANSS negative or general psychopathology subscale scores in either LOCF or completer analyses.

Patients in both treatment groups showed an improvement in CGI-C scores, with no significant between-group differences (Figure 3). At endpoint, 39.0% of all patients in the quetiapine group and 41.8% in the risperidone group were rated "much" or "very much" improved (p = .677). For study completers, the proportion of patients in each treatment group rated "much" or "very much" improved on the CGI-C was greater: 64.3% in the quetiapine group and 57.7% in the risperidone group (p = .150).

A multivariate analysis of covariance (controlling for baseline score and site) found no statistically significant differences between treatment groups on cognitive measures (Wilks lambda = 0.96; multivariate F = 1.05, df = 1,190; p = .40). Similarly, there were no significant differences between treatment groups in either PEAT or SSPA scores. Changes from baseline were statistically significant within each group in phonological fluency, trail making, verbal learning, vigilance, and SSPA, but not PEAT scores. These results are presented in detail elsewhere.[28]

Safety/Tolerability

Overall adverse event rates. The incidence of all reported adverse events was 76.3% for quetiapine and 76.6% for risperidone. Adverse events reported as leading to study withdrawal were similar for quetiapine (5.9%) and risperidone (6.9%). Serious adverse events were reported by 14 patients (4.1%) in the quetiapine group and 9 (2.7%) in the risperidone group. There were no fatalities in either treatment group.

The adverse events occurring in ≥ 5% of patients are shown in Table 4. The most commonly reported adverse event in both groups was somnolence, and this occurred in a higher proportion of patients with quetiapine than with risperidone (26.3% and 19.7%, respectively; p = .04). In both quetiapine and risperidone groups, the majority of the somnolence was rated as mild in intensity (in 70% and 65% of patients, respectively), and the mean duration of somnolence was similar (10.5 days [SD = 14.4] and 9.6 days [SD = 11.6], respectively). Most patients did tolerate somnolence; only 2 patients in the quetiapine group and 1 in the risperidone group withdrew from the study as a result of this adverse event. The other frequently reported adverse events in both groups were headache, weight gain, dizziness, and gastrointestinal disturbance. Dry mouth was reported by significantly more patients in the quetiapine group (12.1%) than in the risperidone group (5.1%; p < .01). Dystonia and akathisia rates were each significantly higher among patients treated with risperidone (5.4% and 8.4%, respectively) compared with patients treated with quetiapine (0.3% and 3.8%, respectively; p < .001 for dystonia; p = .016 for akathisia).

Extrapyramidal symptoms. The incidence of spontaneously reported EPS was significantly higher in the risperidone group (21.8%) than in the quetiapine group (12.7%; p = .002). EPS-related adverse events that were reported included neck rigidity, increased salivation, twitching, abnormal gait, akathisia, dyskinesia, dystonia, extrapyramidal syndrome, hypertonia, movement disorder, oculogyric crisis, tardive dyskinesia, and tremor. Thirteen patients in the risperidone group withdrew from the study because of EPS, specifically for akathisia (N = 4), dystonia (N = 6), extrapyramidal syndrome (N = 1), and movement disorder (N = 2). One patient in the quetiapine group withdrew due to tardive dyskinesia. Treatment with quetiapine resulted in greater improvements in AIMS and SAS total scores compared with risperidone, but these differences did not reach statistical significance. In the BARS score, there was a significantly greater improvement with quetiapine compared with risperidone (0.09-point reduction and 0.01-point increase, respectively; p < .05; Figure 4). The percentages of patients taking anticholinergic medications (initiated after baseline) on a p.r.n. basis were similar in the quetiapine and risperidone groups (5.6% and 6.9%, respectively).

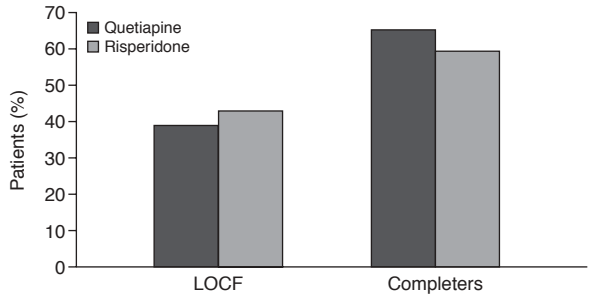
Prolactin levels. There were marked differences in the magnitude and direction of change in prolactin levels associated with quetiapine treatment compared with risperidone. Mean prolactin levels were similar at baseline for quetiapine (22.7 ng/mL) and risperidone (22.6 ng/mL). At the end of the study, mean prolactin levels had decreased by 11.5 ng/mL with quetiapine and increased by 35.5 ng/mL with risperidone (Figure 5). In each case, these changes were significant versus baseline (p < .001). In women, quetiapine resulted in a 12.7-ng/mL reduction

Table 3. Positive and Negative Syndrome Scale (PANSS) Subscale Scores at Week 8 and Last Observation

	Quetiapine		Risperidone		Difference	
PANSS Factor Score	Baseline, Mean (SD)	Change, LSM (SE)	Baseline, Mean (SD)	Change, LSM (SE)	LSM (SE)	p Value[a]
Positive symptoms						
Completers	23.7 (5.0)	–8.1 (0.5)	24.5 (5.1)	–8.0 (0.5)	–0.2 (0.5)	.751
LOCF	24.4 (5.3)	–4.5 (0.4)	24.3 (4.9)	–5.6 (0.4)	1.0 (0.5)	.031
Negative symptoms						
Completers	23.4 (6.5)	–6.0 (0.5)	23.4 (6.0)	–5.6 (0.5)	–0.4 (0.6)	.433
LOCF	23.5 (6.7)	–3.7 (0.4)	23.2 (6.0)	–4.1 (0.4)	0.4 (0.4)	.351
General psychopathology						
Completers	44.0 (10.4)	–13.1 (0.9)	44.9 (10.2)	–12.0 (0.9)	–1.1 (0.9)	.209
LOCF	45.2 (10.8)	–7.0 (0.7)	44.6 (10.0)	–8.2 (0.7)	1.1 (0.8)	.148
Anxiety factor						
Completers	3.4 (1.3)	–1.3 (0.1)	3.4 (1.3)	–1.1 (0.1)	–0.2 (0.1)	.260
LOCF	3.4 (1.2)	–0.7 (0.1)	3.4 (1.2)	–0.8 (0.1)	0.0 (0.1)	.904
Depression factor						
Completers	3.1 (1.3)	–1.0 (0.1)	3.1 (1.3)	–0.9 (0.1)	–0.1 (0.1)	.512
LOCF	3.1 (1.3)	–0.7 (0.1)	3.2 (1.3)	–0.6 (0.1)	–0.1 (0.1)	.222

[a]Superiority analysis.
Abbreviations: LOCF = last observation carried forward, LSM = least squares mean.

Figure 3. Proportion of Patients Rated "Much" or "Very Much" Improved on CGI-C[a]



[a]No significant difference between treatment groups.
Abbreviations: CGI-C = Clinical Global Impressions-Change, LOCF = last observation carried forward.

Table 4. Adverse Events Occurring in ≥ 5% of Patients

	Quetiapine (N = 338)		Risperidone (N = 334)		
Adverse Event	N	%	N	%	p Value[a]
Somnolence	89	26.3	66	19.7	.044
Headache	51	15.1	56	16.7	.599
Weight gain	48	14.2	45	13.4	.824
Dizziness	48	14.2	32	9.6	.0737
Dry mouth	41	12.1	17	5.1	< .01
Dyspepsia	22	6.5	26	7.8	.552
Nausea	21	6.2	22	6.6	.876
Pain	20	5.9	24	7.2	.536
Asthenia	17	5.0	14	4.2	.714
Agitation	17	5.0	10	3.0	.238
Pharyngitis	15	4.4	24	7.2	.140
Akathisia	13	3.8	28	8.4	.016
Vomiting	13	3.8	18	5.4	.364
Dystonia	1	0.3	18	5.4	< .001

[a]Fisher exact test, unadjusted.

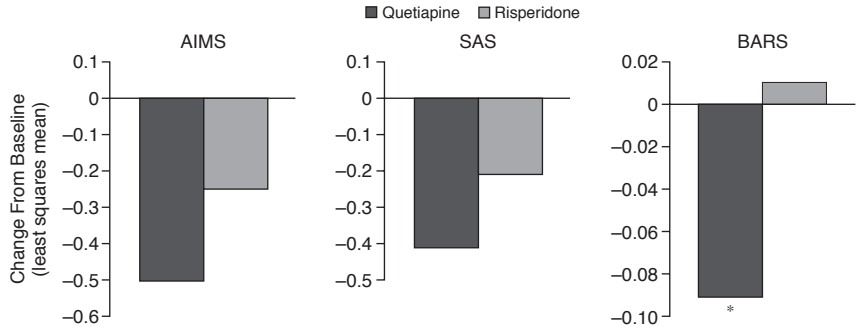
in prolactin levels compared with a 60.9-ng/mL increase with risperidone ($p < .001$). The direction of prolactin change was similar for men, but of a lesser magnitude ($p < .001$; Figure 5). The final mean prolactin levels were similar for men and women in the quetiapine group (11–15 ng/mL); in the risperidone group, the final mean prolactin levels were 91 ng/mL for women and 31 ng/mL for men.

Further analysis of prolactin levels revealed that, in patients treated with quetiapine, the mean change from baseline ranged from –25.98 ng/mL at doses of < 200 mg/day to –11.35 ng/mL at doses of > 600 mg/day. For risperidone-treated patients, the mean change from baseline in prolactin levels ranged from +9.33 ng/mL at doses of < 2 mg/day to +36.98 ng/mL at doses of > 6 mg/day.

Spontaneous reports of sexual and reproductive adverse events were significantly more frequent with risperidone (4.2%) than with quetiapine (0.6%; $p = .002$). Adverse events reported in the risperidone group included lactation (2 patients), menorrhagia (1 patient), dysmenorrhea (4 patients), vaginitis (1 patient), abnormal sexual function (1 patient), anorgasmia (1 patient), impotence (3 patients), and ejaculatory dysfunction (1 patient). Two patients in the quetiapine group reported dysmenorrhea.

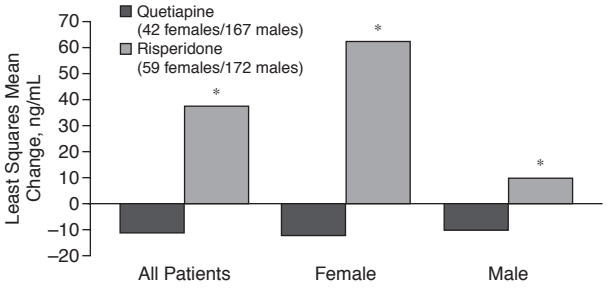
Weight change. There was no significant difference between treatment groups in change in body weight during this 8-week study. Overall, there was a mean weight gain of 1.64 kg for quetiapine-treated patients and 2.12 kg for risperidone-treated patients ($p = .366$). Among completers, the mean weight gain was 2.33 kg and 2.06 kg for quetiapine and risperidone, respectively ($p = .758$). Overall, there was a mean increase of 0.41 (SD = 1.215) in body mass index (BMI) for quetiapine-treated patients and 0.41 (SD = 1.170) for risperidone-treated patients. Among completers, there was a mean increase in BMI of 0.55 (SD = 1.423) and 0.46 (SD = 1.397) in quetiapine- and risperidone-treated patients,

Figure 4. Extrapyramidal Symptoms Rating Scales: Change From Baseline



*p < .05 vs. risperidone.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, SAS = Simpson-Angus Scale.

Figure 5. Prolactin Levels: Change From Baseline



*p < .001 vs. quetiapine.

respectively. Clinically significant weight gain, defined as a ≥ 7% increase from baseline in body weight, occurred in 10.4% of quetiapine-treated patients and 10.5% of risperidone-treated patients.

Mean changes from baseline in random serum glucose concentrations were similar for quetiapine (3.9 mg/dL) and risperidone (4.5 mg/dL) in the LOCF analysis (p = .81). Among patients who completed the study, the changes in random serum glucose concentrations were 1.8 mg/dL for quetiapine and 5.6 mg/dL for risperidone (p = .232). There were no cases of new-onset diabetes mellitus in either group.

DISCUSSION

The results of this 8-week, prospective, comparative study demonstrate that quetiapine and risperidone were similarly efficacious in treating acutely exacerbated patients with chronic schizophrenia. This conclusion is based on the absence of significant differences between treatment groups on the primary efficacy measure (change in PANSS total scores) in both LOCF and completers analyses. Among the analyses of secondary endpoints, both treatment groups had a comparable response rate (≥ 40% reduction in PANSS total and subscale scores) and comparable improvements in PANSS negative and general psychopathology subscale scores in both LOCF and completers analyses, and similar proportions of patients in each treatment group showed significant clinical improvement (CGI-C scores < 3).

Risperidone-treated patients had a significantly greater improvement in PANSS positive subscale score compared with quetiapine-treated patients, but the significant difference between risperidone and quetiapine in PANSS positive subscale scores was only apparent in the LOCF analysis (i.e., including patients who withdrew from the study). Among the completers, there were no significant differences in PANSS positive subscale scores between the 2 treatment groups, although it was the completers in whom the largest decreases in scores occurred, emphasizing that the greatest improvements were seen in those patients who continued with their medication until study completion.

The dose ranges used in this study (quetiapine 200–800 mg/day; risperidone 2–8 mg/day) were based on the product labels.[29,30] The flexible-dose design allowed the trial investigators to adjust the dose based on patients' clinical response and tolerability. Determining the optimal therapeutic dose of an atypical antipsychotic is critically important. Dosing trend surveys have shown that the mean dose of quetiapine has increased from 262 mg/day in 1999 to 389–620 mg/day in 2002.[31–33] The dose of risperidone, on the other hand, has mixed dosing trends. While some studies indicate an increase from 4.9 mg/day to 5.3 mg/day,[31] others have shown a decrease from 4.2 mg/day to 3.4 mg/day.[32] Expert consensus guidelines on therapeutic dosing regimens for the acute treatment of patients with schizophrenia indicate 500 to 800 mg/day for quetiapine and 4 to 6.5 mg/day for

risperidone.[4] The mean median doses observed in this study concur with these guidelines.[4]

The mean median doses of quetiapine achieved by responders (574 mg/day) and completers (626 mg/day) in this study are consistent with recent studies that suggest the optimal therapeutic dose of quetiapine for the treatment of schizophrenia is about 600 mg/day.[5,9,15,16,34–38] This is supported by a number of recent studies that demonstrated comparable efficacy of quetiapine and risperidone, in which the mean dose ranged from 574 mg/day to 580 mg/day for quetiapine and from 4.1 mg/day to 4.9 mg/day for risperidone.[15,16,34] Furthermore, the Comparison of Atypicals in First Episode (CAFE) study in patients experiencing a first episode of schizophrenia found no significant differences in the number of patient withdrawals due to lack of efficacy when quetiapine was dosed at 506 mg/day and risperidone at 2.4 mg/day.[39] In the recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study in patients with chronic schizophrenia, both quetiapine and risperidone (at doses of 543 mg/day and 3.9 mg/day, respectively) were also shown to have comparable withdrawal rates due to lack of efficacy.[40]

In contrast, patients who withdrew due to lack of efficacy in the quetiapine group in this trial had a mean median dose of 429 mg/day, while patients in the risperidone group who withdrew due to lack of efficacy had a mean median dose of 4.7 mg/day. In this subset, there was little difference in the length of time on treatment with quetiapine (14.9 [10.8] days) versus risperidone (15.2 [11.6] days). As the median of patient median doses in this subset was 400 mg/day for quetiapine, or 4.5 mg/day for risperidone, most quetiapine patients who withdrew for lack of efficacy seemed to have had a median dose lower than that observed to be therapeutic, while most risperidone patients seemed to have reached therapeutic median dose.

At the doses given in the present study, quetiapine and risperidone were generally well tolerated in this patient population and had similar overall rates of adverse events. Adverse events reported as leading to attrition were low for both quetiapine (5.9%) and risperidone (6.9%).

Somnolence was one of the most commonly reported adverse events in both treatment groups, and this concurs with reports from other studies.[5,7] Rates of somnolence in our study were higher in patients treated with quetiapine than in patients treated with risperidone; however, somnolence usually occurred early in the study and was generally mild in intensity. A majority of patients became tolerant to this adverse event, and somnolence alone seldom led to study withdrawal. These observations are consistent with the findings of a retrospective analysis of 77 quetiapine studies.[41]

The significantly higher rates of EPS and study withdrawal due to EPS seen in patients treated with risperidone compared with quetiapine are consistent with results from earlier studies.[7,12,16] However, there was no difference in SAS scores, or in the number of patients requiring concomitant anticholinergic medication between the 2 treatment groups, possibly due to the fact that the mean median dose of risperidone was kept below 6 mg/day, or the possibility that clinicians were not sensitive in their assessment of EPS. The lack of significant difference in the SAS scores between the 2 treatment groups may be due to the short duration of the study. In particular, the AIMS includes tardive dyskinesia, any change in which would need to be measured over a longer time period than the duration of this trial in order to achieve significance.

The markedly elevated prolactin levels in patients treated with risperidone in this study are consistent with prior reports,[7,42] as are the reduced prolactin levels seen in patients treated with quetiapine.[43,44] The higher rates of sexual and reproductive function–related adverse events in the risperidone group are consistent with results of other studies which suggest that the risk of sexual dysfunction is significantly greater with risperidone than with quetiapine.[15,45]

The dose-related increase in serum prolactin levels observed in the present study with risperidone, but not quetiapine, is also consistent with prior reports.[7,42] The percentage of risperidone-treated patients in the present study who received the highest dose of > 6 mg/day (29.6%) may have contributed to the magnitude of prolactin elevation seen in this treatment group. As the incidence of EPS with risperidone is also dose-related,[46,47] it could be speculated that, in a similar way, the percentage of patients on the highest doses of risperidone in the present study might be contributing to the incidence of EPS in the risperidone group. However, as the relationship between dose and EPS was not examined, this possibility cannot be confirmed.

Our results differentiate quetiapine from risperidone on the basis of lower rates of EPS and reduced prolactin levels, particularly in women. It has been suggested that this difference may be due in part to the receptor-binding profile of quetiapine and its unique manner of modulating dopamine receptors.[48,49] Unlike some other atypical antipsychotics, quetiapine rapidly dissociates from the dopamine D_2 receptor, allowing normal surges in dopamine to overcome receptor blockade in the nigrostriatal pathway, resulting in a lower risk of EPS. Similar effects on the tuberoinfundibular dopamine pathway may contribute to lower liability to cause hyperprolactinemia. Alternatively, elevations in prolactin levels may be due to the differing abilities of atypical antipsychotics to cross the blood-brain barrier. Higher D_2 receptor occupancies of these drugs in peripheral regions (the pituitary) compared with central regions (the striatum) might explain why some atypical antipsychotics, such as risperidone or

amisulpride, when dosed within the clinical range, can elevate prolactin to a higher degree than other atypicals, such as quetiapine and olanzapine.[50]

Weight gain and hyperglycemia associated with the use of some antipsychotics can be marked and may pose a significant health risk.[51] There was no significant difference between treatment groups in the change from baseline on weight in this study, and neither quetiapine nor risperidone were associated with significant weight gain or with elevation of random serum glucose level. However, the short-term design of this study, as well as the measurements of random rather than fasting glucose concentrations, may hinder an interpretation of these findings.

Several of the usual limitations associated with the clinical comparison of 2 psychoactive drugs apply to this trial. Without a placebo treatment arm, the results cannot be interpreted with certainty to mean that either active treatment is effective. However, the hypothesis that was tested and subsequently proven in this trial was that the efficacy of quetiapine was equivalent (i.e., noninferior) to risperidone. The efficacy of both quetiapine and risperidone has been demonstrated conclusively in previous placebo-controlled studies,[5,10,14] and thus this study avoided the potential risk attendant with exposing acutely psychotic patients to placebo.[52] A second limiting factor associated with the design of this study, and one that has salience for clinicians, is the relatively short-term course of treatment. Although a carefully designed and monitored 8-week course of therapy will demonstrate efficacy, a full clinical response may not be seen for an additional period of weeks or months. Studies that include a long-term extension phase may be warranted to generate comparative long-term efficacy and tolerability data for the 2 compounds.

CONCLUSION

This study demonstrated that quetiapine and risperidone each had similar overall efficacy in treating patients with schizophrenia. The improvements in PANSS total scores and in PANSS negative and general psychopathology subscale scores were comparable with the 2 treatments. Risperidone resulted in greater improvement than quetiapine in PANSS positive subscale score among all patients (LOCF), but not among completers. Both treatments improved the cognitive and social function of this patient population. Changes in body weight and serum glucose were minimal and similar for patients in both treatment groups. While somnolence (generally mild) was more common in patients treated with quetiapine, EPS and hyperprolactinemia were each significantly higher in patients treated with risperidone.

Drug names: carbamazepine (Tegretol and others), clozapine (Fazaclo, Clozaril, and others), erythromycin (Ery-Tab and others), ketoconazole (Nizoral and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

Financial disclosure: Dr. Sweitzer is an employee of AstraZeneca, and Dr. Zhong is a former employee of AstraZeneca. Dr. Hamer's spouse is retired from Bristol-Myers Squibb and has stock options that could eventually be worth more than $10,000; Dr. Hamer and/or his spouse own stock in Bristol-Myers Squibb, Johnson & Johnson, and GlaxoSmithKline, each worth under $10,000; and Dr. Hamer has been a consultant for or is involved in University of North Carolina grants or contracts funded by Ortho-McNeil, Pfizer, Quintiles, Schwartz Pharma, Jazz, Wyeth, Somerset, GlaxoSmithKline, Forest, AstraZeneca, Xcel, Janssen, SAS Institute, and Corcept Therapeutics. Dr. Lieberman has received grant/research support from AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, and Pfizer; has been a consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Novartis, and Pfizer; has participated in advisory boards of AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Pfizer; and holds a patent from Repligen.

This study involved the participation of the following investigators: S. Aaronson (Baltimore, Md.); L. Adler (New York, N.Y.); E. Allan (Montrose, N.Y.); J. Ananth (Torrance, Calif.); M. Bari (Chula Vista, Calif.); N. Bark (Bronx, N.Y.); J. Baron (Houston, Tex.); B. Bastani (Beachwood, Ohio); L. Beckett (Oklahoma City, Okla.); M. Bernstein (Vancouver, Wash.); J. G. Booker (Shreveport, La.); J. Borenstein (Holliswood, N.Y.); D. Brown (Austin, Tex.); J. Canive (Albuquerque, N.M.); J. Carr (Glendale, Calif.); Y.-C. Chan (Columbus, Ohio); J Csernansky (St. Louis, Mo.); D. C. D'Souza (New Haven, Conn.); R. Dahmes (New Orleans, La.); R. McCarthy (White Plains, N.Y.); J. Downs (Memphis, Tenn.); P. Ettigi (Richmond, Va.); J. Ferguson (Salt Lake City, Utah); J. Gamez (Miami Beach, Fla.); J. Gilliam (Richmond, Va.); S. Glass (Clementon, N.J.); R. Gopalan (Falls Church, Va.); W. Granger (Reno, Nev.); B. Harris (Scottsdale, Ariz.); S. Hatti (Media, Pa.); S. Houser (Media, Pa.); P. Hicks (Waco, Tex.); K. Hopper (Waco, Tex.); M. Hubsher (Summit, N.J.); N. Iqbal (Bronx, N.Y.); A. Joseph (Richmond, Va.); A. Karim (Hawthorne, Calif.); Z. E. Kayatekin (Worcester, Mass.); R. Knapp (Park, Fla.); J. G. Kyser (Nashville, Tenn.); M. Lerman (Hoffman Estates, Ill.); R. Litman (Baltimore, Md.); H. E. Logue (Birmingham, Ala.); A. Lowy (Washington, D.C.); P. Maiden (Torrance, Calif.); J. Matthews (Boston, Mass.); J. McEvoy (Butner, N.C.); R. McGuckin (Anaheim, Calif.); H. Meltzer (Nashville, Tenn.); C. Merideth (San Diego, Calif.); R. Mitchell (Virginia Beach, Va.); R. Mofsen (St. Louis, Mo.); T. Okamoto (Santa Ana, Calif.); K. Pahlavan (West Allis, Wis.); T. Porter (Prairie Village, Kan.); S. Preskorn (Wichita, Kan.); W. Privitera (Austin, Tex.); S. Reddy (Oceanside, N.Y.); C. Reist (Long Beach, Calif.); D. Rice (Kirkland, Wash.); N. Richtand (Cincinnati, Ohio); R. Riesenberg (Atlanta, Ga.); S. Riggio (Bronx, N.Y.); M. Rosenthal (San Diego, Calif.); L. Rubenfaer (New Baltimore, Mich.); D. Sack (Cerritos, Calif.); R. Sanders (Pittsburgh, Pa.); J. Schmitz (Kansas City, Mo.); S. Segal (North Miami, Fla.); R. Shiwach (Terrell, Tex.); N. Steinberg (Chagrin Falls, Ohio); R. Steinbook (Miami, Fla.); R. Tait (St. Louis, Mo.); A. Tapp (Tacoma, Wash.); T. Tran-Johnson (San Diego, Calif.); D. Walling (Long Beach, Calif.); J. Williams (Lyons, N.J.); A. Winokur (Farmington, Conn.); J. Wolberg (Bronx, N.Y.); T. Zelnik (Ann Arbor, Mich.).

REFERENCES

1. Conley RR, Kelly DL. Current status of antipsychotic treatment. Curr Drug Targets CNS Neurol Disord 2002;1:123–128
2. Expert Consensus Guideline Series: Treatment of Schizophrenia. J Clin Psychiatry 1999;60(suppl 11):1–80
3. Lehman A, Steinwachs D. Translating research into practice: the schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. Schizophr Bull 1998;24:1–10
4. Kane JM, Leucht S, Carpenter D, et al. Expert Consensus Guideline Series. Optimizing pharmacologic treatment of psychotic disorders: medication selection, dosing, and dose equivalence. J Clin Psychiatry 2003;64(suppl 12):21–51
5. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel"

  © Copyright 2006 Physicians Postgraduate Press, Inc.

(quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. Biol Psychiatry 1997;42:233–246
6. Bouchard RH, Merette C, Pourcher E, et al. Longitudinal comparative study of risperidone and conventional neuroleptics for treating patients with schizophrenia. The Quebec Schizophrenia Study Group. J Clin Psychopharmacol 2000;20:295–304
7. Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. Am J Psychiatry 2001;158:765–774
8. Copolov DL, Link CG, Kowalcyk B. A multicentre, double-blind, randomized comparison of quetiapine (ICI 204,636, "Seroquel") and haloperidol in schizophrenia. Psychol Med 2000;30:95–105
9. Emsley RA, Raniwalla J, Bailey PJ, et al. A comparison of the effects of quetiapine ("Seroquel") and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. PRIZE Study Group. Int Clin Psychopharmacol 2000; 15:121–131
10. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58:538–546
11. Möller H-J, Bauml J, Ferrero F, et al. Risperidone in the treatment of schizophrenia: results of a study of patients from Germany, Austria, and Switzerland. Eur Arch Psychiatry Clin Neurosci 1997;247:291–296
12. Mullen J, Jibson MD, Sweitzer D, QUEST Study Group. A comparison of the relative safety, efficacy, and tolerability of quetiapine and risperidone in outpatients with schizophrenia and other psychotic disorders: The Quetiapine Experience with Safety and Tolerability (QUEST) Study. Clin Ther 2001;23:1839–1854
13. Schulz SC, Thomson R, Brecher M. The efficacy of quetiapine vs haloperidol and placebo: a meta-analytic study of efficacy. Schizophr Res 2003;62:1–12
14. Small JG, Hirsch SR, Arvanitis LA, et al. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. Seroquel Study Group. Arch Gen Psychiatry 1997;54:549–557
15. Knegtering R, Castelein S, Bous H, et al. A randomized, open-label study of the impact of quetiapine versus risperidone on sexual functioning. J Clin Psychopharmacol 2004;24:56–61
16. Reidel M, Moller H-J, Strassnig M, et al. Efficacy and safety of quetiapine versus risperidone in the treatment of negative symptoms. Presented at the 157th annual meeting of the American Psychiatric Association; May 1–6, 2004; New York, NY
17. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
18. Guy W. Clinical Global Impressions Scale. In: Schutte NS, Malouff JM, eds. Sourcebook of Adult Assessment: Applied Clinical Psychology. New York, NY: Plenum Press; 1995:461–465
19. Cornblatt BA, Lenzenweger MF, Erlenmeyer-Kimling L. The continuous performance test, identical pairs version, 2: contrasting attentional profiles in schizophrenic and depressed patients. Psychiatry Res 1989;29:65–85
20. Reitan RM, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation, 2nd ed. Tucson, Ariz: Neuropsychology Press; 1993
21. Spreen O, Strauss E. A Compendium of Neuropsychological Tests and Norms. 2nd ed. New York, NY: Oxford University Press; 1998
22. Gladsjo JA, Schuman CC, Evans JD, et al. Norms for letter and category fluency: demographic corrections for age, education, and ethnicity. Assessment 1999;6:147–178
23. Kohler CG, Turner TH, Gur RE, et al. Recognition of facial emotions in neuropsychiatric disorders. CNS Spectr 2004;9:267–274
24. Patterson TL, Moscona S, McKibbin CL, et al. Social skills performance assessment among older patients with schizophrenia. Schizophr Res 2001; 48:351–360
25. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970; 212:11–19
26. Munetz MR, Benjamin S. How to examine patients using the Abnormal Involuntary Movement Scale. Hosp Community Psychiatry 1988;39: 1172–1177
27. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
28. Harvey P, Patterson TL, Potter LS, et al. Improvement in social competence with short-term atypical antipsychotic treatment: randomized, double-blind comparison of quetiapine vs risperidone for social competence, social cognition, and neuropsychological functioning. Am J Psychiatry. In press
29. AstraZeneca. Seroquel (quetiapine fumarate) tablets. US prescribing information. Available at: http://www.astrazeneca-us.com/pi/Seroquel.pdf. Accessed November 2005
30. Eli Lilly and Company. Zyprexa olanzapine tablets. US prescribing information. E. Available at: http://pi.lilly.com/us/zyprexa-pi.pdf. Accessed Nov 2005
31. Gutierrez B, Zhao Z, Wang PF, et al. Schizophrenia dosing of atypical antipsychotics for inpatients with schizophrenia. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; Washington, DC. Abstract NR177. Available at: http://www.psych.org/edu/other_res/lib_archives/archives/meetings/2003nra.htm. Accessibility verified June 1, 2006
32. International Medical Systems National Database and Therapeutic Index. Plymouth Meeting, Pa: IMS Health; Jan 2001–Dec 2004
33. Citrome L, Jaffe A, Levine J, et al. Dosing of quetiapine in schizophrenia: how clinical practice differs from registration studies. J Clin Psychiatry 2005;66:1512–1516
34. Keks NA, Tonso M, Tabone K, et al. Clinical experience with the atypical antipsychotic quetiapine ("Seroquel") in an acute inpatient unit. Presented at the 24th Collegium Internationale Neuro-Psychopharmacologicum; June 20–24, 2004; Paris, France
35. De Nayer A, Windhager E, Irmansyah, et al. Efficacy and tolerability of quetiapine in patients with schizophrenia switched from other antipsychotics. Int J Psychiatry Clin Pract 2003;7:59–66
36. Kopala L, Milliken H, Whitehorn D, et al. Long-term clinical effectiveness of quetiapine in first episode psychosis [abstract]. Eur Neuropsychopharmacol 2004;14(suppl 3):S266
37. Mavreas V, Christodoulopoulou A, Karokis A, et al. Assessment of the impact of quetiapine treatment on psychopathology, health related quality of life and disability in patients with schizophrenia in Greece. The SQUARE study. Presented at the 9th annual international meeting of the International Society for Pharmacoeconomics and Outcomes Research; May 16–19, 2004; Arlington, Va
38. Sirota P, Panet I, Koren A, et al. Quetiapine versus olanzapine for the treatment of negative symptoms in patients with schizophrenia. Hum Psychopharmacol Clin Exp. In press
39. Lieberman J, McEvoy JP, Perkins D, et al. Comparison of atypicals in first-episode psychosis: a randomized, 52-week comparison of olanzapine, quetiapine, and risperidone [abstract]. Eur Neuropsychopharmacol 2005;15(suppl 3):S525
40. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs on patients with chronic schizophrenia. N Engl J Med 2005; 353:1209–1223
41. Goldstein JM, Zhong K. Tolerance to somnolence: preclinical mechanisms and clinical evidence with quetiapine. Presented at the 43rd annual meeting of the American College of Neuropsychopharmacology; Dec 12–16, 2004; San Juan, Puerto Rico
42. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997;17:407–418
43. Atmaca M, Kuloglu M, Tezcan E, et al. Quetiapine is not associated with increase in prolactin secretion in contrast to haloperidol. Arch Med Res 2002;33:562–565
44. Fric M, Laux G. Prolactin levels and symptoms of hyperprolactinemia in patients treated with amisulpride, risperidone, olanzapine and quetiapine [in German]. Psychiatr Prax 2003;30(suppl 2):97–101
45. Bobes J, Garc A-Portilla MP, Rejas J, et al. Frequency of sexual dysfunction and other reproductive side-effects in patients with schizophrenia treated with risperidone, olanzapine, quetiapine, or haloperidol: the results of the EIRE study. J Sex Marital Ther 2003;29:125–147
46. Peuskens J, for the Risperidone Study Group. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Br J Psychiatry 1995;166:712–726
47. Tarsy D, Baldessarini RJ, Tarazi FI. Effects of newer antipsychotics on extrapyramidal function. CNS Drugs 2002;16:23–45
48. Kapur S, Zipursky R, Jones C, et al. A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. Arch Gen Psychiatry 2000;57:553–559
49. Goldstein JM. Mechanism of action of quetiapine: a modulator of

dopamine at the D_2 receptor. Presented at the 43rd annual meeting of the American College of Neuropsychopharmacology; Dec 12–16, 2004; San Juan, Puerto Rico
50. Kapur S, Langlois X, Vinken P, et al. The differential effects of atypical antipsychotics on prolactin elevation are explained by their differential blood-brain disposition: a pharmacological analysis in rats. J Pharmacol Exp Ther 2002;302:1129–1134
51. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Diabetes Care 2004;27:596–601
52. Charney DS, Nemeroff CB, Lewis L, et al. National Depressive and Manic-Depressive Association consensus statement on the use of placebo in clinical trials of mood disorders. Arch Gen Psychiatry 2002; 59:262–270