Cognitive Functioning and Acute Sedative Effects of Risperidone and Quetiapine in Patients With Stable Bipolar I Disorder: A Randomized, Double-Blind, Crossover Study

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Objective: Antipsychotic medications differ in their sedative potential, which can affect cognitive performance. The primary objective of this double-blind study was to compare the effects of treatment initiation with risperidone and quetiapine on cognitive function in subjects with stable bipolar disorder.

Method: Subjects had a DSM-IV diagnosis of bipolar I disorder in partial or full remission and a Young Mania Rating Scale score ≤ 8 at screening. Subjects were randomly assigned to 1 of 2 treatment sequences: risperidone-quetiapine or quetiapine-risperidone. Subjects in the risperidone-quetiapine sequence received 2 mg of risperidone with dinner and placebo with breakfast during period 1 and 100 mg of quetiapine with dinner and 100 mg with breakfast during period 2. Subjects in the quetiapine-risperidone sequence received the same treatments in reverse order. The 2 treatment periods were separated by a 6- to 14-day washout period. Cognitive function, including attention, working memory, declarative memory, processing speed, and executive functions, was measured before and after dosing. The Visual Analog Scale for Fatigue was also completed. The primary endpoint was a neurocognitive composite score (NCS). The study was conducted from November 2004 through August 2005.

Results: Thirty subjects were randomly assigned; 28 took all doses of study medication and completed a baseline and at least 1 postbaseline assessment in each treatment. On the NCS, significantly better overall cognitive function was seen after risperidone than after quetiapine at each time point after dosing. Subjects performed significantly better after risperidone than after quetiapine ($p < .05$) on 9 of the 18 individual cognitive outcome measures and significantly better after quetiapine than after risperidone on 1 measure. Sleeping or the need for sleep during the test days was reported in significantly more patients after receiving quetiapine than risperidone.

Conclusions: The results indicate that initiation of quetiapine treatment was associated with more immediate adverse cognitive effects and increased somnolence than risperidone treatment.

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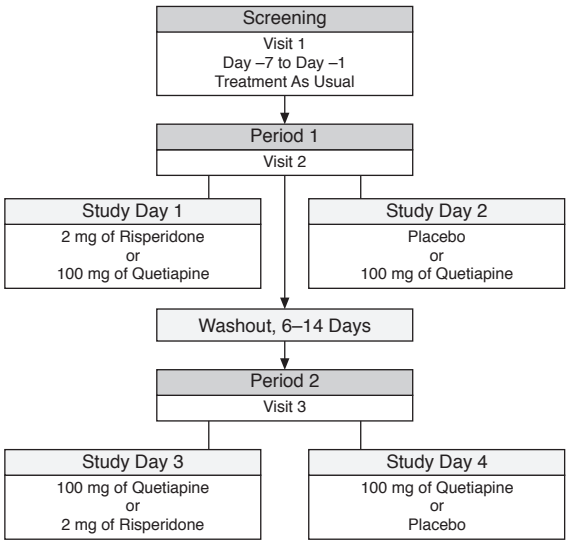
Medication-induced sedation is associated with drowsiness, reduced wakefulness, slowed brain activity, and impaired cognitive performance[1] and thus can be problematic for many persons who are employed, operate a motor vehicle, or have other responsibilities. Somnolence has been reported as a prominent adverse event in bipolar patients receiving risperidone or quetiapine, both as monotherapy and as an adjunct to mood stabilizers, for the treatment of bipolar mania.[2–9] Somnolence in these studies was recorded only from the patients' self-reports and its incidence tended to vary from study to study. Moreover, the severity of somnolence was not

Figure 1. Study Design for Randomized, Double-Blind, Crossover Study of Risperidone and Quetiapine in Patients With Stable Bipolar I Disorder



quantified in those previous studies, nor were potential sedative effects on cognitive function assessed.

The purpose of this double-blind crossover study was to evaluate cognitive functioning, perceived sedation, and somnolence in stable bipolar patients initiating treatment with an atypical antipsychotic (risperidone or quetiapine). Both medications are indicated for the short-term treatment of acute manic or mixed episodes of bipolar I disorder and were selected for comparison because of their wide current use in the treatment of bipolar disorder.

A wide-ranging assessment of cognitive function was performed in the present study, including some domains previously shown to be affected by pharmacologic agents with sedative effects. Also included was a self-rated assessment of fatigue and vigor and subjects' need for sleep after receiving risperidone or quetiapine.

METHOD

Eligible subjects were aged 18 to 55 years. Subjects were required to have a diagnosis of bipolar I disorder in partial or full remission, as defined by the DSM-IV criteria and by clinical evaluation by the principal investigator. A bipolar I disorder diagnosis in partial or full remission was further confirmed by a current Young Mania Rating Scale[10] total score ≤ 8, no manic episode over the preceding 6 months, and, if the subject was receiving a mood stabilizer, no significant changes in dose over the preceding 2 months. Subjects were required to be in a state of remission for this study because the symptoms of acute mania would have confounding effects on their ability to complete the cognitive test battery. Eligible subjects were also required to complete the Cogtest Workstation Orientation (Cogtest Inc., London, United Kingdom) during the screening visit to ensure testing continued only for subjects capable of generating valid and interpretable data. Subjects were excluded from participation in the study if they had current use of sedating medications (e.g., benzodiazepines, prescription or herbal sleep agents, antihistamines); current symptoms of depression (Montgomery-Asberg Depression Rating Scale[11] score > 12); or current diagnoses of major depressive disorder, mania, hypomania, psychosis, dysthymia, or catatonic behaviors (as determined by use of the Mini-International Neuropsychiatric Interview[12]), all of which were considered to be potential confounders.

After providing informed consent and completing the diagnostic procedure and the screening assessments, subjects were randomly assigned to 1 of the 2 treatment sequences (risperidone-quetiapine or quetiapine-risperidone) during study periods 1 and 2 (Figure 1). The final protocol was reviewed and approved by an appropriately constituted institutional review board according to specifications outlined in the U.S. Code of Federal Regulations (CFR). The study was conducted from November 2004 through August 2005.

Dosing

The recommended dosing regimens of these 2 antipsychotics are based on their pharmacokinetics: risperidone is routinely administered once daily at night and quetiapine twice daily. After oral administration of risperidone, the time to peak plasma concentrations ranges from 0.8 to 1.4 hours, while the combined elimination half-life of risperidone plus its active metabolite, 9-hydroxyrisperidone, is about 20 hours.[13,14] Oral quetiapine reaches peak plasma concentrations in approximately 1.5 hours, with a mean elimination half-life of 2 to 3 hours.[14] According to the manufacturers' guidelines for each of the 2 treatments, once-daily dosing of risperidone and twice-daily dosing of quetiapine are recommended for the treatment of bipolar mania.[15,16]

Risperidone is approved for the treatment of bipolar disorder at a starting dose of 2 to 3 mg once daily and quetiapine at a starting dose of 50 to 100 mg twice daily. Dose levels used in usual clinical practice for bipolar disorder were estimated from a recent retrospective analysis of a managed-care claims database that indicated the mean daily doses of risperidone and quetiapine in bipolar disorder were 2 mg and 182 mg, respectively.[17] Subjects randomly assigned to the risperidone-quetiapine sequence received 2 mg of risperidone with dinner and placebo with breakfast during period 1, and 100 mg of quetiapine with dinner and 100 mg with breakfast during period 2. Subjects randomly assigned to the quetiapine-risperidone sequence received the quetiapine doses during period 1 and the risperidone dose during period 2. Thus, the selected starting

doses of 2 mg of risperidone and 200 mg of quetiapine and the frequency and timing of dosing that were used in this study are consistent with labeling and clinical practice.

Subjects currently receiving psychotropic medications continued to receive these medications at doses and frequencies as prescribed by their treating physicians. Concomitant medications were required to have been at stable doses over the preceding 8 weeks. Use of caffeine and nicotine was allowed at each subject's customary use.

Period 1

Study day 1. Baseline cognitive tests and the self-rated assessment of fatigue and vigor were completed at 10:00 a.m. and 3:00 p.m. At 6:00 p.m., subjects were randomly assigned to 1 of 2 treatment sequences, risperidone-quetiapine or quetiapine-risperidone, followed by the first dose of study medication (2 mg of risperidone for sequence risperidone-quetiapine or 100 mg of quetiapine for sequence quetiapine-risperidone). Medications were taken with a meal. The subjects stayed at the testing site overnight in order to ensure compliance with the treatments in the research protocol.

Study day 2. At 8:30 a.m., subjects received the morning dose of study drug (placebo or 100 mg of quetiapine). Cognitive tests and the self-rated assessment of fatigue and vigor were completed at 10:00 a.m., 12:30 p.m., and 3:00 p.m.

Washout Period

Subjects received no study medications during a washout period of 6 to 14 days between periods 1 and 2.

Period 2

On study days 3 and 4, the subjects completed the identical procedures as on study days 1 and 2, except that the treatments were reversed: those who had received risperidone during period 1 now received quetiapine, and those who had received quetiapine in period 1 now received risperidone.

Cognitive Tests

The primary endpoint was derived from 8 computerized neurocognitive tests chosen for the specific aspects of cognitive performance that are measured by each test. The tests included: (1) AX Continuous Performance Test[18,19]; (2) Identical Pairs Continuous Performance Test, 4-digit version[20–22]; (3) Flanker Continuous Performance Test[23]; (4) Auditory Digit Span[24–27]; (5) Auditory Number Sequencing[28]; (6) Strategic Target Detection[29,30]; (7) Word List Memory[31,32]; and (8) Symbol Digit Substitution.[33,34] Each test generates a series of dependent variables (e.g., reaction time, ability to distinguish targets from nontargets, total experiment time, and number of correct responses). The 8 computerized tests provided 18 test variables for analysis. The computer test system that was used (Cogtest, Cogtest Inc., London, United Kingdom) has not yet been formally validated for the assessment of sedation.

The tests were administered to the subjects via computer in the above order. Subjects were required to perceive visual stimuli presented on a computer monitor; respond to auditory tone and word stimuli presented through a computer system speaker and headphones; and use touch-screen, computer mouse, and keyboard to complete the tests. Site coordinators were trained to administer portions of the Auditory Number Sequencing and Word List Memory tests. Each subject had the tests administered by the same study coordinator at each testing session across study periods.

Primary Endpoint

The primary endpoint was a neurocognitive composite score (NCS) derived from the 18 test variables. A composite score was selected for the primary endpoint because of the differences between the 8 tests in their potential sensitivity to sedation. The NCS is the arithmetic mean of the standardized scores of the 18 cognitive test variables. For each test variable, standardization used the means and standard deviations (SD) of the morning baseline values from periods 1 and 2 from the combined sample of subjects in this study.

All scores were coded such that a positive change from baseline in NCS denotes improved cognitive function and a negative change denotes deteriorated cognitive function.

Secondary Endpoints

Secondary endpoints were obtained by aggregating the 18 cognitive test variables into 5 domains: processing speed, attention, working memory, declarative memory, and executive function. These domains, which were recommended by the developers of the computerized testing system, were chosen on the basis of the domains' sensitivity to adverse effects associated with motor or cognitive slowing and sedation.[35–38] A domain score was defined as the mean of the standardized test variable scores in that domain. Treatment differences on each of the 18 test variables were also analyzed and are reported here. A summary of the 5 domains, 18 test variables, and 8 cognitive tests is presented in Table 1.

Subjects' assessments of sedation were measured by the Visual Analog Scale for Fatigue (VAS-F).[39] The scale has been validated in a study of fatigue and sleep disorders.[39] The VAS-F is a paper and pencil test that comprises 18 individual visual analog scales that evaluate different aspects of fatigue (13 items) and vigor (5 items). Subscale scores for fatigue and vigor are computed as the means of the items within the subscales, with scores ranging from 0 to 10.

Table 1. The 5 Domains, 18 Test Variables, and 8 Cognitive Tests Used to Assess Cognitive Functioning and Acute Sedative Effects in Patients With Stable Bipolar I Disorder[a]

Test Variable by Domain	Test
Processing speed	
1. Mean reaction time of correct detections	1. AX Continuous Performance Test
2. Mean reaction time of correct detections for all conditions	2. Flanker Continuous Performance Test
3. Total experiment time	3. Strategic Target Detection
Attention	
4. Probability of correct discriminations	1. AX Continuous Performance Test
5. Total correct forward	4. Auditory Digit Span
6. Total correct within 90 seconds	5. Symbol Digit Substitution
7. Probability of correct discrimination	6. Identical Pairs Continuous Performance Test
8. Sum correct	2. Flanker Continuous Performance Test
Working memory	
9. Total correct backwards	4. Auditory Digit Span
10. Total correct sequences	7. Auditory Number Sequencing
Declarative memory	
11. Percentage trial-to-trial transfer	8. Word List Memory
12. Delayed recall correct	8. Word List Memory
13. Delayed recognition discrimination	8. Word List Memory
Executive function	
14. Response bias	1. AX Continuous Performance Test
15. Response bias	6. Identical Pairs Continuous Performance Test
16. Response delay for incongruent stimuli	2. Flanker Continuous Performance Test
17. Total perseverative errors	3. Strategic Target Detection
18. Strategic efficiency	3. Strategic Target Detection

[a]The neurocognitive composite score is the mean of all 18 test variables after standardization. Domain scores are the mean of the standardized test variable scores for the domain.

Table 2. Background Characteristics of the 28 Subjects With Stable Bipolar I Disorder

Characteristic	Risperidone-Quetiapine Sequence (N = 14)	Quetiapine-Risperidone Sequence (N = 14)	Total (N = 28)
Sex, N			
Men	11	9	20
Women	3	5	8
Age, mean ± SD, y	41.8 ± 6.1	39.9 ± 8.7	40.9 ± 7.4
Race/ethnicity, N			
Black	10	7	17
White	2	7	9
Other	2	0	2
DSM-IV diagnosis, N			
Hypomanic or manic episode			
Partial remission	0	1	1
Full remission	2	1	3
Major depressive episode			
Partial remission	0	1	1
Full remission	9	10	19
Mixed episode in full remission	2	0	2
Current or most recent episode in full remission, N	1	1	2
Years since diagnosis, mean ± SD[a]	9.8 ± 6.0	10.2 ± 7.9	10.0 ± 6.9
YMRS total score, mean ± SD	2.3 ± 2.1	3.4 ± 2.2	2.9 ± 2.2
MADRS total score, mean ± SD	5.2 ± 3.8	6.1 ± 3.5	5.6 ± 3.6

[a]N = 26.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

Daytime Sleep

Sleeping and the need for sleep throughout the post-dose test day were assessed by spontaneous reports of adverse events of drowsiness or sleepiness or by subject self-report between testing sessions. Subjects were asked, "Have you slept or have you felt the need for sleep since receiving the morning dose of study medication [or since completing the morning or midday assessments]?"

Data Analysis

Neurocognitive composite score change scores were tested in a mixed-effects crossover analysis of covariance model including fixed effects for sequence; treatment; period; time; and treatment-by-time, sequence-by-time, and period-by-time interactions and a random subject effect. The initial model was reduced to a final model by removing interaction terms with p values > .10. Between-

Table 3. Mean Neurocognitive Composite Score at Baseline and 3 Study Time Points in Subjects After Receiving Risperidone or Quetiapine

Time Point	Risperidone (N = 28), Mean ± SD	Quetiapine (N = 28), Mean ± SD	Least Squares Mean[a] (Risperidone minus Quetiapine), 95% CI	p Value[a]
Baseline	–0.01 ± 0.41	0.00 ± 0.47	…	…
Postdose				
10:00 am	0.09 ± 0.32	–0.25 ± 0.51	0.35 (0.21 to 0.48)	< .0001
12:30 pm	0.10 ± 0.41	–0.27 ± 0.56	0.38 (0.19 to 0.56)	.0003
3:30 pm	0.09 ± 0.33	0.03 ± 0.35	0.12 (0.01 to 0.23)	.0333

[a]Least squares mean differences and p values are from analysis of covariance models with fixed effects for baseline, sequence, period, and treatment and a random effect for subject.
Symbol: … = not applicable.

treatment differences were tested by time point when treatment-by-time interactions were significant. Secondary endpoints (5 domain scores, scores on the 18 cognitive tests, and VAS-F fatigue and vigor subscale scores) were analyzed using the same mixed-model procedures. Effect sizes (i.e., Cohen's "d": the difference between treatments in terms of pooled SD units) were calculated for the NCS and domain scores. Treatment differences in the need for sleep were assessed by the Mainland-Gart test for matched proportions in crossover designs.

RESULTS

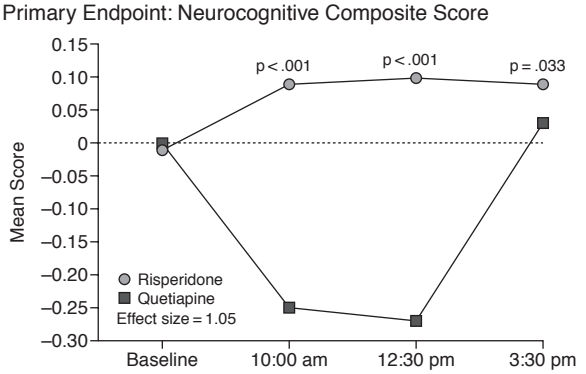
Thirty subjects were randomly assigned to the risperidone-quetiapine or quetiapine-risperidone sequence. Both study periods were completed by 28 of the 30 subjects. Reasons for discontinuation were consent withdrawal (1 subject) and noncompliance (1 subject). The background characteristics of subjects assigned to the 2 sequences were similar (Table 2). The bipolar disorder was in partial remission in 2 subjects and in full remission in 26 of the 28 subjects.

Concomitant psychotropic medication use was the same during the 2 study periods. Lithium, selective serotonin reuptake inhibitors, other antidepressants, and other antiepileptics were each received by 3 subjects; unspecified antidepressants by 2 subjects; and a benzodiazepine by 1 subject.

Primary Endpoint (NCS)

The treatment-by-time interaction was significant (p = .007), indicating that the between-treatment differences in mean NCS change scores varied between the assessment time points. Treatment differences were significant at each time point after dosing. Scores worsened after dosing with quetiapine and were unchanged after risperidone (Table 3, Figure 2). The standardized effect size for the difference between treatments on NCS was 1.05.

Figure 2. Mean Neurocognitive Composite Scores (primary endpoint) in Patients Receiving Risperidone or Quetiapine[a]



[a]The statistics are calculated on the basis of least squares means adjusted for baseline values.

Secondary Endpoints

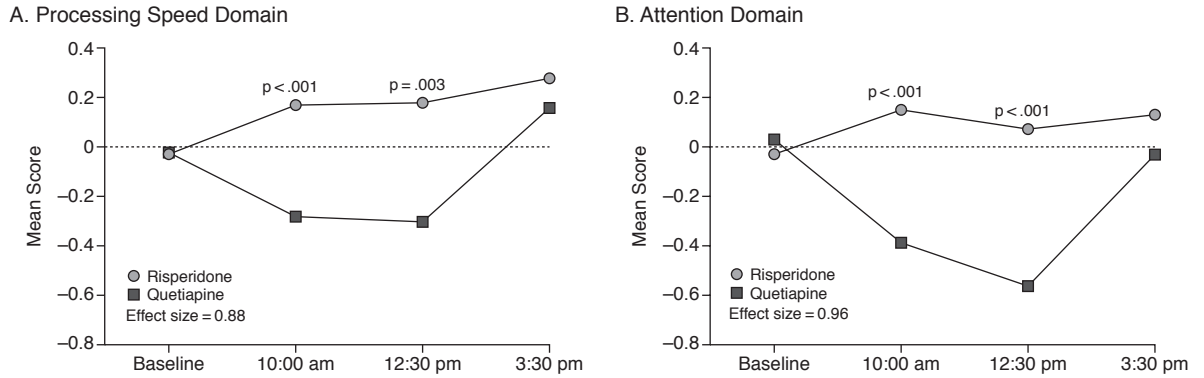
Processing speed and attention. Domain scores for processing speed and attention are presented in Figures 3A and 3B. The treatment-by-time interactions were significant (both p = .001), indicating that the between-treatment differences in mean NCS change scores varied between the assessment time points. Significant between-treatment differences in processing speed and attention were seen at 10:00 a.m. and 12:30 p.m. after dosing. Function improved after dosing with risperidone and deteriorated after dosing with quetiapine at these 2 time points. The standardized effect sizes for processing speed and attention were 0.88 and 0.96, respectively.

Working memory and declarative memory. The treatment-by-time interactions were not significant (not shown). Therefore, the mean between-treatment differences across all time points were analyzed and they were statistically significant: the difference in working memory (least squares means) was 0.32 (p = .01) and the difference in declarative memory was 0.27 (p = .002).

Executive function. Between-treatment differences were not significant (not shown).

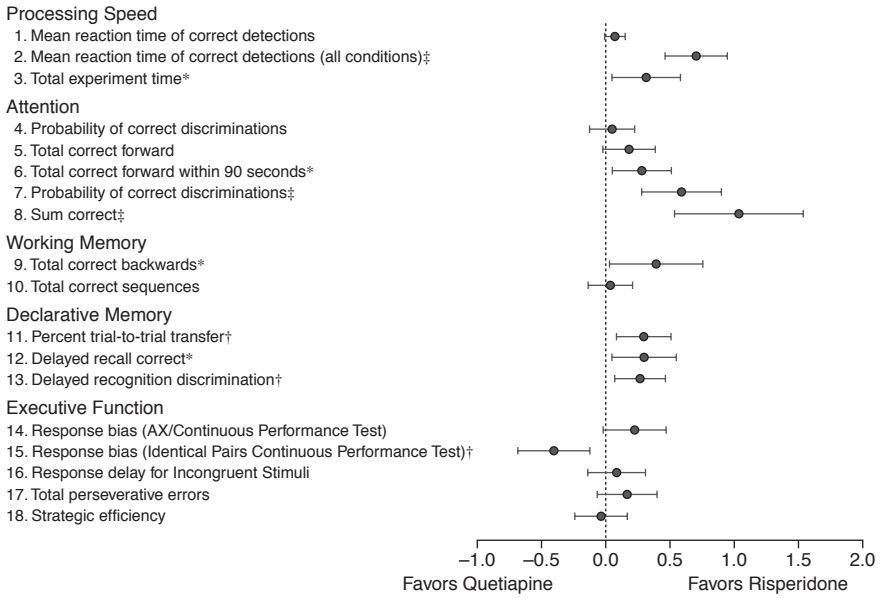
Test variables. Figure 4 presents the mean between-treatment differences across all time points for the 18 test variables. Subject performance, as measured on 9 test variables (mean reaction time of correct detections, total experiment time, total correct forward within 90 seconds, probability of correct discrimination, sum correct, total

Figure 3. Mean Scores on the Processing Speed and Attention Domains in Subjects Receiving Risperidone or Quetiapine[a]



[a]The statistics are calculated on the basis of least squares means adjusted for baseline values.

Figure 4. Estimated Differences in Responses (risperidone minus quetiapine) (least squares means and 95% confidence intervals)



*p < .05.
†p < .01.
‡p < .001 between treatments.

correct backwards, percentage trial-to-trial transfer, delayed recall correct, and delayed recognition discrimination) was significantly better after risperidone treatment. Subject performance as measured on the test variable response bias (Identical Pairs Continuous Performance Test) was significantly better after quetiapine treatment. Between-treatment differences on the remaining 8 test variables were not statistically significant.

VAS-F fatigue and vigor subscales. Significant between-treatment differences were noted at the first 2 time points (Table 4). Risperidone treatment was associated with less fatigue and more vigor than was treatment with quetiapine.

Daytime Sleep

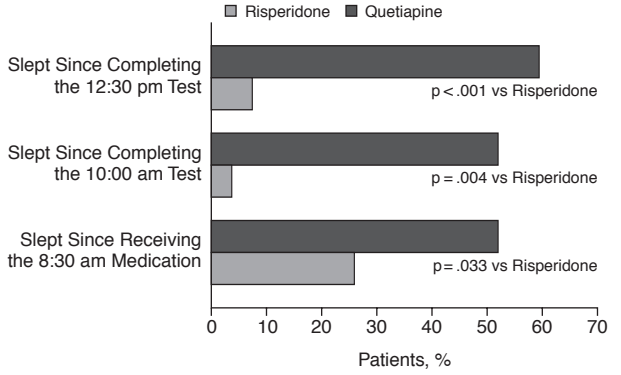
At 10:00 a.m., 26% of the subjects treated with risperidone reported having slept since the morning dose (placebo in the morning) compared with 52% of subjects treated with quetiapine (p = .033); at 12:30 p.m., 4% and 52% of subjects, respectively, reported that they had slept since the 10:00 a.m. assessments (p = .004), and at 3:30 p.m., 7% and 59%, respectively, reported that they

Table 4. Mean Visual Analog Scale for Fatigue-Fatigue and -Vigor Subscale Scores in Subjects After Receiving Risperidone or Quetiapine

Time Point	Risperidone (N = 28), Mean ± SD	Quetiapine (N = 28), Mean ± SD	Least Squares Mean[a] (Risperidone minus Quetiapine), 95% CI	p Value[a]
Fatigue				
Baseline	3.19 ± 1.86	3.61 ± 2.09	…	…
Postdose				
10:00 am	4.10 ± 2.46	5.71 ± 2.36	–1.42 (–2.43 to –0.40)	.008
12:30 pm	3.82 ± 2.55	5.98 ± 2.28	–1.94 (–3.14 to –0.75)	.003
3:30 pm	3.77 ± 2.48	4.39 ± 2.28	–0.33 (–1.14 to 0.48)	.405
Vigor				
Baseline	5.28 ± 2.04	5.23 ± 2.10	…	…
Postdose				
10:00 am	4.59 ± 2.47	3.31 ± 2.20	1.26 (0.23 to 2.30)	.019
12:30 pm	4.61 ± 2.40	3.61 ± 2.11	0.98 (0.06 to 1.91)	.038
3:30 pm	4.76 ± 2.36	4.22 ± 2.27	0.53 (–0.18 to 1.23)	.135

[a]Least squares mean differences and p values are from analysis of covariance models with fixed effects for baseline, sequence, period, and treatment and a random effect for subject.
Symbol: … = not applicable.

Figure 5. Subjects Who Reported Sleeping After Receiving the 8:30 a.m. Medication and After the 2 Testing Sessions, %



had slept since the 12:30 p.m. assessments ($p < .001$) (Figure 5).

Safety

Adverse events were reported in significantly more subjects after receiving quetiapine than risperidone (Table 5). The most substantial difference between treatments was in the incidence of somnolence, reported in 9 subjects after risperidone treatment and in 24 subjects after quetiapine treatment ($p < .05$).

Table 5. Treatment-Emergent Adverse Events in Subjects Receiving Risperidone or Quetiapine

Variable	Risperidone (N = 29)	Quetiapine (N = 29)
Total adverse events	18	36
Subjects with ≥ 1 event	14	25*
Somnolence	9	24*
Fatigue	4	6
Dry mouth	0	3
Headache	2	0
Carpal tunnel syndrome	1	0
Dystonia	1	0
Nausea	1	0
Blurred vision	0	1
Nasal congestion	0	1

*$p < .05$ vs. risperidone.

DISCUSSION

Treatment initiation with risperidone for clinically stable patients with bipolar I disorder was associated with significantly better cognitive functioning (as measured by the NCS) and fewer adverse events than treatment with quetiapine. The standardized effect size for NCS (1.05) is considered a "large" effect and very likely corresponds to a clinically meaningful between-treatment difference. The mean change from baseline on the NCS in the patients after treatment initiation with quetiapine was 0.25 to 0.27 standard deviations below baseline performance, indicating that at least 20% of the patients worsened by at least 0.5 standard deviations. A change of 0.5 standard deviations is generally considered to be clinically relevant. Two of the 5 domains (processing speed and attention) followed the same pattern that was observed with the NCS and yielded similar statistical results. Standardized effect sizes for these domains were also large ($d = 0.88–0.96$). At the individual test level, subjects performed significantly better as measured by 9 cognitive test variables after treatment with risperidone. After treatment with quetiapine, subjects performed better as measured on only 1 test variable. Treatment differences as measured by the other 8 of the individual cognitive test variables were not statistically significant. In light of these individual test results, the overall effect observed on the NCS is notable. The composite score results were robust when combining the performance scores on all tests, including those that may not be sensitive to the effects of sedation.

The subjects' self-assessments on the VAS-F scale appeared to reflect the findings from the primary endpoint

analysis. Subjects reported less fatigue and more vigor after receiving risperidone than quetiapine. Significantly fewer subjects reported sleeping or needing to sleep after risperidone than after quetiapine during the postdose study days.

Several study design choices and limitations need to be addressed. We attempted to mimic clinical practice with the dosing of the medications in order to quantify and compare the first-day-of-treatment effects on cognitive function. The doses and frequency of administration of the tested drugs approximate those specified in product labeling and used in clinical practice for initiation of bipolar treatment. The doses evaluated are at the low end of the range used for subsequent treatment (1–6 mg/day of risperidone, 200–800 mg/day of quetiapine), and this study does not address proportional effects that may occur at up to 3 times the dose of risperidone or 4 times the dose of quetiapine. Because the cognitive assessments were performed closer in time to the quetiapine dosing than the risperidone dosing, it may not be unexpected for the effects of sedation to be more readily detected after quetiapine dosing. Our study was designed to measure the effects on cognitive function that clinicians and patients can expect to see directly after treatment is started with risperidone or quetiapine, and the dosing regimens studied are commonly employed. Future research should be conducted to compare cognitive performance after morning and evening dosing regimens for both medications and to examine the effects of tolerance to sedation over time on these outcomes.

It was not considered practical to conduct a study evaluating cognitive measures of this type in acutely manic patients. Therefore, although stable bipolar outpatients receiving longer-term treatment are a population of interest, these findings may not be generalizable to acutely ill patients. The observed differences between the active treatment arms indicate significant differences in their effects on overall cognitive functioning when the treatments are taken as usually prescribed. In this crossover design, the same patients were tested on each medication in a randomized order. Therefore, differences in individual susceptibility to the effects of sedation cannot be responsible for the results found.

It should be noted that the construct and labeling of the 5 cognitive domains used in this study are not consistent with the domains defined by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery.[40] The MATRICS guidelines, however, were not available at the time this study protocol was designed. We acknowledge that the choice of cognitive domains for this study, though defined a priori, might be considered suboptimal by some investigators. Use of an alternate selection of tests could conceivably yield a different pattern of results. To address this concern, we analyzed and provided results on each test variable, regardless of its assignment to any particular domain.

Last, establishing the true clinical significance of statistically significant cognitive test score changes would require large-scale validation in relevant samples. This has not been done in bipolar disorder. Only in dementia research has the clinical significance of specific cognitive test score changes been well validated.[41,42] In these studies, change of approximately 0.5 SD (i.e., an effect size $d \sim 0.50$) has been validated as being clinically observable and possibly linked to other indicators such as health care costs. Some investigators have suggested that the 0.5 SD effect size may be a "universal" yardstick to mark clinically meaningful change across many different kinds of measures,[43] and similar degrees of change have been used in studies of cognitive change in schizophrenia.[44] In the current study, the difference in scores is more than double this threshold, suggesting it is a large difference between treatments that is likely to be detectable by patients, clinicians, and other observers.

These findings may not be generalizable to acutely ill patients with bipolar I disorder, who are more likely to have antipsychotics treatment initiated. However, there is little information on how to choose an antipsychotic for treating these patients. Our results suggest that quetiapine is associated with adverse cognitive effects (as measured by the NCS) and increased sedation (as measured by subject self-report on the VAS-F scale and adverse event reporting) relative to risperidone. These factors should be considered and may be particularly important for patients with bipolar I disorder who desire rapid return to their previous social and vocational pursuits.

While not evaluated in our study, prior work[45–48] has established high rates of treatment noncompliance in bipolar I disorder, and adverse effects, including cognitive impairment and sedation, may be prominent reasons for discontinuation, particularly if these effects may impair driving and other functions in otherwise high-functioning persons. Our study examined only acute effects at low doses, and long-term or higher dosing may not be associated with the same adverse effects documented here. However, bipolar I disorder has been characterized by frequent discontinuation and thus acute effects (from stopping and restarting treatment) may be more common than treating physicians can control. Although some physicians may choose a medication because it has sedating effects, this choice should not be made without recognizing the associated cognitive impairment.

Drug names: quetiapine (Seroquel), risperidone (Risperdal).

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