Efficacy of Quetiapine and Risperidone Against Depressive Symptoms in Outpatients With Psychosis

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Background: The treatment of psychotic symptoms in patients with mood disorders is a complex challenge. Antipsychotic medications in these individuals may be associated with extrapyramidal symptoms (EPS), worsening of depression, and functional impairment. Atypical antipsychotics such as quetiapine and risperidone are associated with a decreased incidence of adverse events such as EPS. The objective of this study was to compare the efficacy and tolerability of quetiapine and risperidone for the treatment of depressive symptoms in outpatients with psychosis.

Method: In this 4-month, multicenter, open-label trial, patients were randomly assigned in a 3:1 ratio of quetiapine to risperidone, and both drugs were flexibly dosed. Eligible patients had psychoses and demonstrated 1 of several DSM-IV diagnoses, including schizoaffective disorder, bipolar I disorder, major depressive disorder, delusional disorder, Alzheimer's dementia, schizophreniform disorder, vascular dementia, and substance abuse dementia. Patients were classified as mood disordered if they had bipolar disorder, major depressive disorder, or schizoaffective disorder. Efficacy was assessed using the Positive and Negative Syndrome Scale and the Clinical Global Impressions scale. The Hamilton Rating Scale for Depression (HAM-D) was used to assess the level of depressive symptoms. The primary tolerability assessment was presence or absence of substantial EPS, defined as EPS severe enough to require an alteration in treatment.

Results: A total of 554 patients were randomly assigned to quetiapine and 175 to risperidone. Mean doses at 16 weeks were 318 mg for quetiapine and 4.4 mg for risperidone. Although both agents produced improvements in mean HAM-D scores, quetiapine produced a greater improvement than risperidone in all patients ($p = .0015$). Within the mood-diagnosed population, incidences of both substantial EPS ($p = .001$) and at least moderate EPS ($p = .0373$) occurred significantly less frequently among patients taking quetiapine. For patients with non-mood diagnoses, incidences of substantial EPS were fewer for patients taking quetiapine than for those taking risperidone ($p = .062$); however, this was not statistically significant.

Conclusion: These results suggest that quetiapine may be a useful agent in the management of depressive symptoms in patients with psychosis.

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Depressive symptoms are common in patients with schizophrenia and may contribute to the 20-fold higher incidence of suicide in this population compared with the general population.[1] Affective disorders in patients with schizophrenia are generally associated with poor outcome, with an increased risk of relapse and a high rate of suicide.[1] In serious mood disorders, such as bipolar depression, the suicide rate is 30 times higher than that of the general population.[2] Thus, treatment of coexisting affective and psychotic symptoms is a complex clinical challenge.

Antipsychotics are commonly added to the treatment regimen for patients with psychotic mood disorders.[3,4] However, antipsychotic medications in these individuals may be associated with extrapyramidal symptoms (EPS), possible worsening of depression, and functional impairment.[5–7]

Recent evidence suggests that atypical antipsychotics may produce an antidepressant effect that could be beneficial in the treatment of depressive symptoms in patients with schizophrenia.[1,8] Compared with conventional antipsychotics, atypical antipsychotics may have superior efficacy for the treatment of schizophrenia with mood symptoms.[9] Additionally, preliminary evidence supports the usefulness of atypical antipsychotics in treating depressive symptoms associated with psychotic and depressive disorders.[10] Because atypical antipsychotics are associated with a decreased incidence of EPS,[11] these medications may have more overall advantages compared with typical antipsychotics.[9,12,13] Quetiapine, in particular,

appears to have low potential for EPS at all dosing ranges[14] and in all populations, including the elderly[15–17] and adolescents.[18]

Quetiapine and risperidone are 2 atypical antipsychotics currently used in the United States for the treatment of patients with schizophrenia and other psychotic disorders. The objective of the present study was to compare the efficacy and tolerability of quetiapine and risperidone for the treatment of depressive symptoms in outpatients with psychotic disorders. This is a subanalysis of data on mood symptoms from the quetiapine experience with safety and tolerability (QUEST) study. The results of the analysis of primary endpoints on psychosis, tolerability, and EPS from the QUEST study are described in another article.[19]

METHOD

Study Design

In this 4-month, multicenter, open-label trial, patients were randomly assigned in a 3:1 ratio of quetiapine to risperidone. Patients completed 7 office visits at weeks 0, 1, 2, 4, 8, 12, and 16.

Both quetiapine and risperidone were flexibly dosed. Patients randomly assigned to quetiapine began with a total daily dose of 50 mg, with upward titration in 50-mg to 100-mg increments every 1 to 2 days. The maximum dose of quetiapine was 800 mg/day.

Patients randomly assigned to risperidone began with 1 mg b.i.d. with increases in increments of 1 mg b.i.d. on days 2 and 3 as tolerated, to a target dose of 3 mg b.i.d. Further dose adjustments, if indicated, occurred at intervals of not less than 1 week.

For both drugs, investigators were instructed to adjust dosage to meet the clinical needs and response of individual patients. Investigators were also instructed to discontinue previous antipsychotic agents within 1 month of trial entry. Patients who failed to stabilize on either quetiapine or risperidone monotherapy were permitted to return to their original antipsychotics.

Patients

Patients were included if they had psychoses and 1 of the following DSM-IV[20] diagnoses: schizoaffective disorder, bipolar I disorder, major depressive disorder, delusional disorder, Alzheimer's dementia, schizophreniform disorder, vascular dementia, or substance abuse dementia. Diagnoses were made based on clinical interviews administered by site investigators. Other eligibility criteria included no evidence of medically significant disorders, no current treatment with clozapine or history of nonresponsiveness to clozapine, and no history of drug-induced agranulocytosis. Patients were classified as having a mood disorder if they had 1 of the following diagnoses: (1) bipolar disorder, (2) major depressive disorder, or (3) schizoaffective disorder. Patients with schizoaffective disorder were grouped with patients with mood disorders because their pharmacologic treatment was more like that of patients with bipolar disorder or psychotic major depressive disorder (i.e., mood medication plus antipsychotic medication) than that of patients with schizophrenia (i.e., usually antipsychotic monotherapy).

Concurrent Medications

Patients could receive concomitant medications that were deemed clinically indicated by the investigator. Another antipsychotic agent was to be prescribed only after attempts to stabilize the patient on quetiapine or risperidone monotherapy failed over a 1-month period. Long-acting injectable antipsychotics (haloperidol or fluphenazine) and clozapine or olanzapine were prohibited during the study period.

Patients who were taking prescribed mood stabilizers and antidepressants were allowed to continue with those medications if they had been on a stable dose for at least 2 weeks before randomization. Rescue medication (e.g., intramuscular haloperidol, benzodiazepines, or anti-EPS agents) for situations such as extreme agitation, acute psychosis, and EPS was permitted at the discretion of the investigator. EPS assessments were not completed within 24 hours after administration of rescue medication.

Efficacy Assessments

The Positive and Negative Syndrome Scale (PANSS)[21] and the Clinical Global Impressions (CGI) scale[22] were used to evaluate efficacy against psychotic symptoms. The Hamilton Rating Scale for Depression (HAM-D)[23] was used to assess the level of depressive symptoms at weeks 0, 8, and 16. The following HAM-D factors were assessed: factor 1—anxiety/somatization (anxiety psychic, anxiety somatic, somatic symptoms gastrointestinal, somatic symptoms general, hypochondriasis, and insight); factor 2—weight (loss of weight); factor 3—cognitive disturbance (feelings of guilt, suicide, agitation, depersonalization and derealization, paranoid symptoms, obsessive and compulsive symptoms); factor 4—diurnal variation (morning or afternoon severity); factor 5—retardation (depressed mood, work and activities retardation, genital symptoms); and factor 6—sleep disturbance (insomnia early, insomnia middle, and insomnia late).

Two domains on the HAM-D were also assessed: (1) vegetative symptoms (insomnia early, insomnia middle, insomnia late; retardation, agitation, anxiety somatic, somatic symptoms gastrointestinal, somatic symptoms general, genital symptoms, weight loss, diurnal variation present, diurnal variation severity) and (2) nonvegetative symptoms (depressed mood, guilt, suicide, work and activities, anxiety psychic, hypochondriasis, insight, depersonalization and derealization, paranoid symptoms, and obsessional and compulsive symptoms).

EPS Assessments

The primary assessment for tolerability was the presence or absence of EPS to a substantial degree. *Substantial EPS* is defined as requiring 1 or more of the following alterations in treatment: (1) prescription of an anti-EPS medication, (2) reduction in dose of randomized treatment, or (3) discontinuation of the randomized treatment. EPS event information was determined from a symptom checklist created by AstraZeneca (available from AstraZeneca upon request).

Statistical Analysis

The overall differences between treatment with quetiapine and treatment with risperidone in postbaseline last-observation-carried-forward (LOCF) HAM-D score were evaluated using an analysis of covariance (ANCOVA). Treatment differences over time according to diagnosis (mood versus non-mood disorders) were assessed using a repeated-measures ANCOVA. Treatment differences over time stratified by baseline HAM-D score (i.e., < 10, 10 to 19, and ≥ 20) were assessed using a repeated-measures ANCOVA within mood and non-mood diagnostic groups.

HAM-D factor scores were summarized with descriptive statistics. Differences in dose of quetiapine or risperidone at 4 months were analyzed using Dunnett's t test. Incidence of EPS was analyzed using generalized estimating equations and included maximum baseline EPS severity and time as covariate factors.

RESULTS

Patient Demographics

The characteristics of the patients randomly assigned to quetiapine (N = 554) or risperidone (N = 175) are shown in Table 1. Both groups of patients showed similar demographics with mean ages of 45 and 46 years for quetiapine and risperidone, respectively. No statistically significant differences between treatments were found for age, sex, or race. The male/female ratio was 50:50 for quetiapine and 54:46 for risperidone. Mood disorders were diagnosed in 316 (57%) of quetiapine patients and 103 (59%) of risperidone patients.

On study entry, 33.7% of patients were using mood stabilizers, 33.7% were taking antidepressants, 26.5% were taking anxiolytics (including benzodiazepines), 13.6% were taking atypical antipsychotics, and 36%, typical antipsychotics. No significant differences in the continuing use of prior medications were found between treatment groups (p = .17).

Dosing

The dosing of quetiapine over time for the different diagnostic groups is shown in Figure 1. The mean dose received by all the patients at week 16 was 318 mg; however, patients with schizophrenia used significantly more quetiapine at all time periods after 2 weeks than patients with mood disorders (p = .036). At 16 weeks, patients with bipolar disorder used less quetiapine (mean difference = –74 mg, p = .062) than patients with schizophrenia. At 16 weeks, patients with major depressive disorder or schizoaffective disorder used 54 mg and 28 mg, respectively, less than patients with schizophrenia; however, this was not statistically significant (p > .25).

The dosing of risperidone over time for the different diagnostic groups is shown in Figure 2. The mean dose received by all of the patients was 4.4 mg at week 16, and, as with quetiapine, patients with mood disorders required lower doses of risperidone than did patients with schizophrenia (p < .011).

Table 1. Demographic Details

Characteristic	Quetiapine Group (N = 554)	Risperidone Group (N = 175)
Age, mean, y	45.1	46.2
Race, N (%)		
White	402 (73)	131 (75)
African American	94 (17)	28 (16)
Other	58 (10)	16 (9)
Sex, N (%)		
Women	277 (50)	80 (46)
Men	277 (50)	95 (54)
Diagnosis, N (%)		
Bipolar disorder	83 (15)	20 (11)
Major depressive disorder	75 (14)	26 (15)
Schizoaffective disorder	158 (29)	57 (32)
Schizophrenia	218 (39)	67 (38)
All mood diagnoses	316 (57)	103 (59)
All non-mood diagnoses	238 (43)	72 (41)

Efficacy Against Psychotic Symptoms

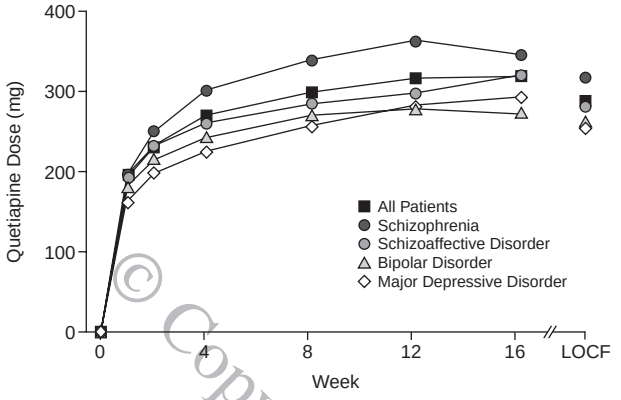
Efficacy against psychotic symptoms was assessed using the PANSS and the CGI. Both quetiapine and risperidone groups showed increasing improvement in clinical condition throughout the trial, according to CGI scores. At trial completion, no significant difference was seen between treatment groups on CGI scores or on PANSS positive scale, negative scale, or total score. These results are reported in full elsewhere.[19]

HAM-D Scores

There was no significant difference in baseline HAM-D scores between quetiapine- and risperidone-treated patients. The mean change from baseline to postbaseline observation in HAM-D score at week 16 (LOCF) was slightly greater (p = .028) in the quetiapine group than in the risperidone group (Figure 3).

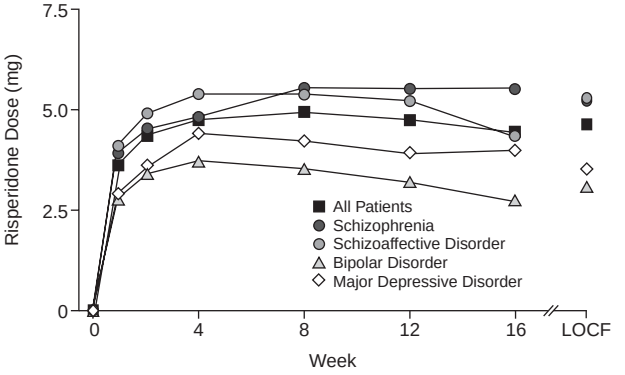
The percentages of changes from baseline for the different diagnostic groups are shown in Table 2. Quetiapine produced a greater improvement in HAM-D scores than did risperidone, both in patients with primary mood disorders and in patients with non-mood disorders.

Figure 1. Mean Quetiapine Dose by Diagnosis[a]



[a]Abbreviation: LOCF = last observation carried forward.

Figure 2. Mean Risperidone Dose by Diagnosis[a]



[a]Abbreviation: LOCF = last observation carried forward.

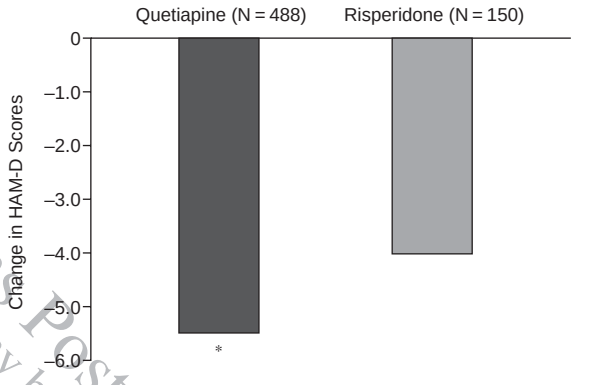
The changes in mean HAM-D scores for patients with and without mood disorders were examined with respect to baseline HAM-D score. In patients with mood disorders and a high baseline HAM-D score (≥ 20), quetiapine produced a significantly greater reduction in HAM-D score than risperidone (–47% vs. –34%, p = .0051, Figure 4A). For patients with mood disorders who had moderate HAM-D scores at baseline (scores of 10 to 19), both drugs were equally effective (–38% vs. –43%, p = .54). For patients with mood disorders who had low baseline HAM-D scores (< 10), neither drug produced a significant improvement or deterioration (–0.1% ± 16.1% vs. –15.2% ± 25.4%, p = .59, for quetiapine and risperidone, respectively).

The changes in HAM-D scores for non-mood disordered patients were similar to the changes seen in mood disordered patients (Figure 4B). For patients with non-mood disorders who had low or moderate baseline HAM-D scores (< 20), there were no significant differences in the improvements produced by quetiapine or risperidone. However, for patients with non-mood disorders and high baseline HAM-D scores (≥ 20), quetiapine produced a significantly greater reduction in mean HAM-D scores than risperidone (p = .008).

The mean changes from baseline for individual HAM-D factor scores are shown in Figure 5. The largest treatment differences (at least 5% of baseline) were in favor of quetiapine over risperidone—these were for HAM-D factors 4 (diurnal variation), 5 (retardation), and 6 (sleep disturbance) and in the vegetative symptom domain. Little difference between quetiapine and risperidone was observed for the HAM-D factors of anxiety/somatization, weight, and cognitive disturbance and in the nonvegetative domain items.

For the group as a whole, patients in the quetiapine group scored significantly better on the retardation, sleep disturbance, and vegetative domain items. Mood disordered patients on quetiapine scored significantly better on retardation and vegetative domains. In patients diagnosed with non-mood disorders, and in patients with factor scores of 0 at baseline, differences were not statistically significant.

Figure 3. Mean Change in HAM-D Scores for All Patients (baseline to postbaseline, last observation carried forward)[a]



[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
*p = .028.

EPS Assessments

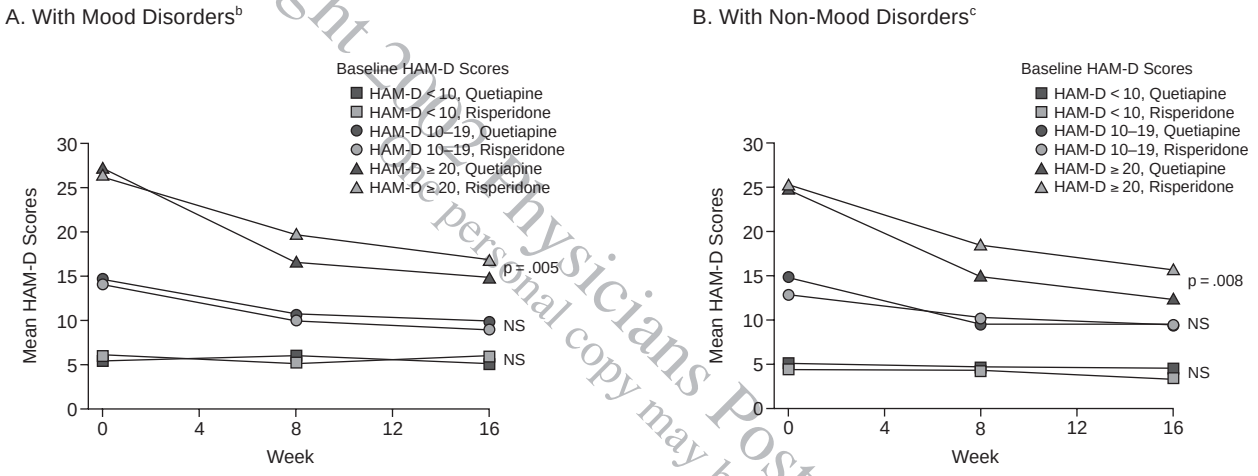
The safety and tolerability of quetiapine and risperidone were compared by examining the incidence of EPS to a substantial degree in the patients diagnosed with either mood disorders (Figure 6) or non-mood disorders. Over the trial period, substantial EPS occurred less frequently among quetiapine-treated patients in both the mood (p < .001) and non-mood (p = .063) diagnosed patients. More of the patients diagnosed with mood disorders and treated with risperidone reported substantial EPS at week 1 (8.3%) compared with the patients with mood disorders treated with quetiapine (1.4%). The incidence of substantial EPS at LOCF was also lower for patients treated with quetiapine (2.9%) compared with patients treated with risperidone (10.1%).

Table 2. Percentages of Change From Baseline HAM-D Scores[a]

Diagnosis	Quetiapine N	Quetiapine Mean Baseline Score	Quetiapine Change (%)	Risperidone N	Risperidone Mean Baseline Score	Risperidone Change (%)	p Value of Difference
All patients	554	15.50	–44.6	175	15.07	–34.4	.0015
All mood diagnoses	316	16.86	–44.1	103	16.58	–35.7	.0364
All non-mood diagnoses	238	13.71	–45.6	72	12.93	–31.1	.0083
Bipolar disorder	83	16.28	–50.4	20	14.60	–33.2	.0956
Major depressive disorder	75	19.11	–42.2	26	20.08	–39.7	.7100
Schizoaffective disorder	158	16.10	–41.6	57	15.74	–34.6	.2149
Schizophrenia	218	13.46	–41.6	67	13.16	–31.4	.0694
Other non-mood[b]	20	16.45	–65.4	5	9.80	–31.1	.0447

[a]Repeated-measures analysis of 2- and 4-month results. Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
[b]A p value is not reliable for this small number of patients with varying diagnoses, including Alzheimer's dementia, delusional disorder, and substance abuse dementia.

Figure 4. Mean HAM-D Scores for Patients With Psychosis From Baseline to Week 16 for Quetiapine and Risperidone[a]



[a]Abbreviations: HAM-D = Hamilton Rating Scale for Depression, NS = nonsignificant.
[b]Mood diagnoses include bipolar disorder, major depressive disorder, and schizoaffective disorder.
[c]Non-mood diagnoses include delusional disorder, Alzheimer's dementia, schizophreniform disorder, vascular dementia, and substance abuse dementia.

In patients diagnosed with mood disorders, the incidence of substantial EPS and at least moderate EPS was significantly less frequent in patients taking quetiapine than in patients taking risperidone ($p < .001$ for substantial EPS, $p = .037$ for moderate EPS).

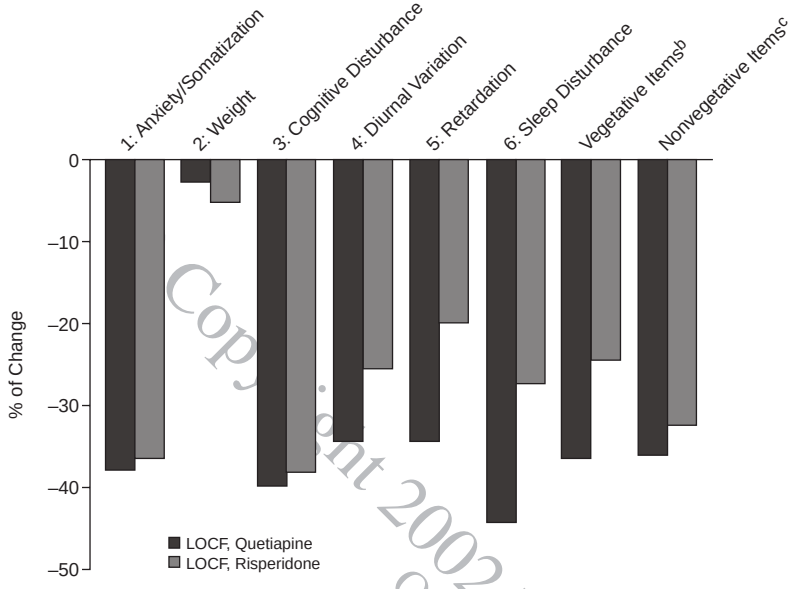
In the subgroup of patients diagnosed with non-mood disorders, substantial EPS was present at week 1 in 2.9% of the patients treated with risperidone, the incidence increased to a peak of 7.8% at month 2, and the overall incidence at LOCF was 4.2%. For quetiapine-treated patients, substantial EPS was present at week 1 in 1.3% of the patients, the incidence subsequently increased to a peak value of 3.5% at month 1, and the overall incidence at LOCF was 3.4% ($p = .063$).

The occurrence of at least moderate hypokinesia or akinesia was rare for both diagnostic groups (3.3% for quetiapine, 9.9% for risperidone). Changes in hypokinesia/akinesia severity and changes in HAM-D scores were found to be correlated and reflected the fact that, on average, both kinesia and mood symptoms improved throughout the study. To rule out a causal link between EPS condition and HAM-D scores, a subset ANCOVA examined patients who had at worst mild akinesia, hypokinesia, or akathisia at baseline and experienced no change in the severity of those 3 symptoms; quetiapine patients still scored significantly better on HAM-D ($p = .017$). No significant difference was found between mood and non-mood diagnoses groups ($p > .40$).

DISCUSSION

This study compared the safety and efficacy of quetiapine and risperidone for the treatment of depressive symptoms in psychotic patients. While both agents produced improvements in mean HAM-D scores, quetiapine produced a greater improvement than did risperidone in

Figure 5. Mean Change From Baseline in HAM-D Composite Factor Scores for Quetiapine and Risperidone[a]



[a]Abbreviations: HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward.
[b]Includes insomnia early, middle, late; retardation; agitation; anxiety somatic; somatic symptoms gastrointestinal; somatic symptoms general; genital symptoms; weight loss; diurnal variation present; and diurnal variation severity.
[c]Includes depressed mood, guilt, suicide, work and activities, anxiety (psychic), hypochondriasis, insight, depersonalization and derealization, paranoid symptoms, and obsessional and compulsive symptoms.

all patients (p = .0015), in patients with primary mood disorders (p = .036), and in patients with non-mood disorders (p = .008). Quetiapine produced a statistically greater effect than risperidone in treating depressive symptoms in those patients with higher initial HAM-D scores. The clinical significance of the changes produced by treatment with quetiapine is not known. The incidence of substantial EPS was lower in patients treated with quetiapine than in patients treated with risperidone. This was statistically significant for mood diagnoses and showed a trend for non-mood diagnoses (p = .062). Both substantial and moderate EPS occurred statistically significantly less frequently among those mood-diagnosed patients who were taking quetiapine.

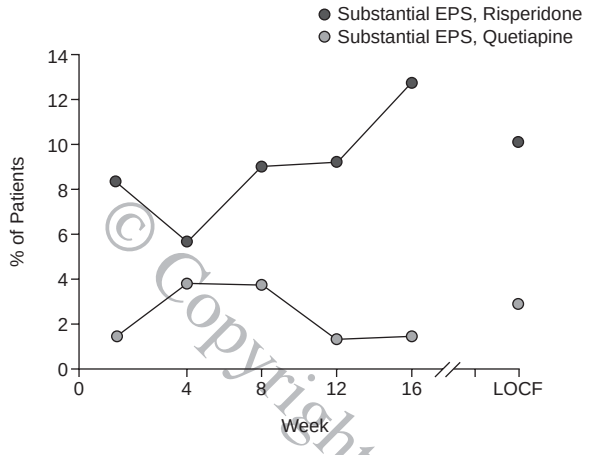
Other groups of investigators have reported that quetiapine and risperidone exhibit efficacy in the treatment of depressive symptoms in patients.[10,24] Sajatovic et al.[25] reported significant improvement on HAM-D scores in 20 individuals with bipolar or schizoaffective disorder who received open-label quetiapine therapy. In a case series of 6 patients with treatment-resistant bipolar disorder treated with quetiapine, 2 patients showed evidence of moderate-to-marked improvement on the Clinical Global Impressions scale modified for bipolar disorder.[26] Sedation was the main side effect noted in the Ghaemi and Katzow report,[26] and the investigators concluded that quetiapine may be a useful treatment for some patients with treatment-resistant bipolar disorder.

A number of open-label studies have investigated the use of risperidone to treat mood disorders with promising results.[27–32] Ostroff and Nelson[29] examined the use of risperidone to augment selective serotonin reuptake inhibitor (SSRI) antidepressants in 8 patients who had not responded to SSRI therapy. The 8 patients showed improvement within 1 week of the addition of risperidone. Vieta et al.[24] reported significant reductions in HAM-D scores for 8 of 10 patients with refractory rapid-cycling bipolar disorder who received open-label risperidone therapy. One double-blind study found risperidone to be as effective as lithium or haloperidol in the treatment of acute mania.[33] Finally, Guille et al.[32] reported that risperidone was as effective as clozapine and olanzapine in the treatment of bipolar disorder.

Induction of mania has been associated with a number of atypical antipsychotics such as risperidone, olanzapine, sertindole, quetiapine, and amisulpride.[34–39] Mania induction was not reported in this study; however, all the patients who were receiving mood stabilizers were permitted to continue this treatment as per protocol. In this analysis and in the larger QUEST study,[19] no mania scale was used; thus, instances of mood induction might not have been detected. Our conclusion of no identified mania induction in this study and in the larger QUEST study, then, is qualified by the small sample size in this study and the limited methodology in the QUEST study.

This study had a flexible-dose design, which allowed clinicians to titrate medications for maximum efficacy and minimum side effects depending upon the needs of each patient. At the time of the trial, risperidone was a U.S. Food and Drug Administration–approved medication and thus had a package insert that specified dosage. Quetiapine was still an investigational drug with optimal dose yet to be determined. Instructions to investigators were identical for both drugs: to titrate dosage according to patients' clinical needs. This dosing plan mirrors what generally occurs in clinical practice and thus provides insight into how study compounds will be used under such conditions. The limitations of this study include the following: (1) this was an open-label clinical trial, with the possibility of investigator and/or patient bias; (2) the trial involved a relatively small number of patients, with correspondingly small numbers of patients with mood and

Figure 6. Incidence of Extrapyramidal Symptoms (EPS) to a Substantial Degree in Patients Diagnosed With Mood Disorders[a]



[a]Substantial EPS is defined as requiring 1 or more of the following alterations in treatment: prescription of an anti-EPS medication, reduction in dose of randomized treatment, a discontinuation of randomized treatment.

non-mood disorders; (3) no standardized diagnostic instrument was used to assign diagnoses to patients; (4) no measurement was made of mania; (5) all patients were psychotic, thus no conclusions can be drawn about patients with bipolar disorder without psychoses; (6) elderly patients were also examined with the HAM-D, although it has been suggested that another scale might be more appropriate (e.g., the Geriatric Depression Screening Scale[40]); and (7) patients were allowed to continue the use of antidepressants and mood medications, thus efficacy and side effects might have been influenced by the concomitant medications.

In conclusion, in this trial, quetiapine produced a greater overall improvement in HAM-D scores compared with risperidone—this was true whether patients had mood or non-mood disorders. Patients with high baseline HAM-D scores improved more than did individuals with lower baseline HAM-D scores. The incidences of substantial EPS were fewer in patients treated with quetiapine compared with patients treated with risperidone. These results suggest that quetiapine may be a useful agent in the management of depressive symptoms in patients with psychotic disorders.

Drug names: clozapine (Clozaril and others), fluphenazine (Prolixin, Permitil, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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