Quetiapine in the Treatment of Anxiety in Patients With Bipolar I or II Depression: A Secondary Analysis From a Randomized, Double-Blind, Placebo-Controlled Study

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Objective: Quetiapine monotherapy shows efficacy in bipolar depression. The analyses in this multicenter, double-blind, randomized, fixed-dose, placebo-controlled study evaluated effects of quetiapine monotherapy on anxiety symptoms in bipolar depression.

Method: Of 542 outpatients randomly assigned to treatment, 539 with bipolar I (N = 358) or bipolar II (N = 181) disorder experiencing a major depressive episode (DSM-IV) received 8 weeks of quetiapine monotherapy (600 or 300 mg/day) or placebo between September 2002 and October 2003. Anxiety assessments included the Hamilton Rating Scale for Anxiety (HAM-A) and relevant items from the Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Rating Scale for Depression (HAM-D). Analyses evaluated the pooled dose groups versus placebo.

Results: At week 8, quetiapine 600 and 300 mg/day each demonstrated significant improvements in HAM-A total score versus placebo (–10.8 and –9.9 vs. –6.7, $p < .001$). Quetiapine (pooled doses) significantly improved HAM-A total score from week 1. In bipolar I depression, quetiapine showed significant improvement in HAM-A total score versus placebo (–10.4 vs. –5.1, $p < .001$). In bipolar I depression, quetiapine also showed significant improvements versus placebo on the HAM-A anxious mood and tension items, HAM-A psychic and somatic subscales, MADRS inner tension item, and HAM-D psychic anxiety item (all $p < .001$), but not the HAM-D somatic anxiety item. In bipolar II depression, quetiapine reduced the HAM-A total score more than placebo, but the difference was not statistically significant (–9.8 vs. –9.0, $p = .473$). In bipolar II depression, quetiapine showed significant improvement versus placebo on the HAM-A anxious mood, MADRS inner tension, and HAM-D psychic anxiety items (all $p < .01$).

Conclusion: Quetiapine monotherapy shows efficacy in treating anxiety symptoms in bipolar I depression; however, the anxiolytic effects in bipolar II disorder require further investigation.

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Individual financial disclosure appears at the end of this article.

A complete list of the principal investigators of the BOLDER Study Group appears at the end of this article.

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Bipolar depression is a recurrent and debilitating phase of bipolar disorder. Patients are affected by depressive symptoms for longer periods than mania or hypomania.[1,2] Bipolar depression is associated with high rates of morbidity and mortality.[3]

Anxiety symptoms are highly prevalent across many mood disorders, including unipolar depression,[4] but have been shown to be more prevalent among patients with bipolar disorder.[5] The National Comorbidity Survey estimated that the lifetime risk of an anxiety disorder in patients with bipolar I disorder was 93%.[6] One recent estimate suggested that 55.8% of patients with bipolar disorder have at least 1 comorbid anxiety disorder.[7] Comorbid anxiety in patients with bipolar disorder is particularly troublesome and can significantly limit successful outcomes by increasing the severity of symptoms, the frequency of episodes, and suicide rates, while reducing response to therapy.[7,8] Moreover, severe anxiety comorbid with depression in patients with bipolar disorder is a predictor of suicide.[9]

Treating the symptoms of anxiety while also relieving depression is an important therapeutic target in the management of patients with anxiety associated with bipolar depression. Recent studies show that comorbid anxiety

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in patients with bipolar disorder is not adequately treated in clinical practice.[10] Treatment of bipolar depression with antidepressants alone (i.e., without a concurrent mood stabilizer), including those that have anxiolytic properties, e.g., selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), may be associated with a possible risk of treatment-emergent mania.[11] This risk in addition to recent evidence that conventional antidepressant use may increase the risk of suicide, particularly in the first 9 days,[12] underscores the need for alternative treatment options for the management of anxiety in bipolar depression.

There are few clinical studies to date that have addressed the treatment of patients with bipolar depression and comorbid anxiety. The atypical antipsychotic olanzapine has demonstrated greater efficacy than placebo in treating bipolar depression.[13] With regard to anxiety symptoms in these patients, olanzapine and olanzapine-fluoxetine both showed a significantly greater mean improvement on the Hamilton Rating Scale for Anxiety (HAM-A) at endpoint compared with placebo (–5.5 [$p = .002$] and –7.0 [$p < .001$] vs. –3.5).[13] Quetiapine has demonstrated efficacy in the treatment of anxiety symptoms in psychiatric disorders other than bipolar depression. In patients with schizophrenia, quetiapine was significantly more effective than placebo at reducing anxiety symptoms.[14] In a small, open-label study of patients with posttraumatic stress disorder (PTSD) ($N = 20$), quetiapine showed significant improvements in anxiety symptoms over 6 weeks.[15] A 9-week, open-label study also indicated preliminary efficacy of quetiapine, in combination with SSRIs, in improving persistent comorbid anxiety symptoms in a small number of patients with a depressive or anxiety disorder ($N = 11$).[16] Similarly, quetiapine plus SSRIs has shown efficacy in patients with obsessive-compulsive disorder.[17]

This study was primarily designed to evaluate the efficacy of quetiapine in treating the depressive symptoms of bipolar disorder, as measured by the mean change from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS).[18] The primary results have been reported elsewhere.[19] Quetiapine (600 mg/day and 300 mg/day) was associated with a significantly greater mean change in MADRS total score from baseline to endpoint compared with placebo (–16.73 and –16.39 vs. –10.26, $p < .001$ for each quetiapine dose [600 mg/day and 300 mg/day, respectively] vs. placebo using last-observation-carried-forward analysis-of-covariance methods). Common adverse events in patients treated with quetiapine versus placebo were dry mouth, sedation or somnolence, dizziness, and constipation. There was minimal weight change, and no patients withdrew from the study due to weight gain. The rate of treatment-emergent mania with quetiapine was no greater than with placebo. Further details of the safety and tolerability results have also been reported previously.[19] One of the secondary objectives of this study was to evaluate the efficacy of quetiapine monotherapy for the treatment of anxiety symptoms associated with major depressive episodes in patients with bipolar disorder. These data are presented in this article.

METHOD

Study Design

This 8-week study was a multicenter, double-blind, randomized, fixed-dose, placebo-controlled, parallel-group evaluation of quetiapine monotherapy (once daily) compared with placebo in adult patients with bipolar I or II disorder experiencing a major depressive episode. The study was carried out at 39 centers in the United States. between September 2002 and October 2003. The design adhered to the current amendment of the Declaration of Helsinki and The International Conference on Harmonisation (ICH)/Good Clinical Practice guidelines. The institutional review boards at each site approved the protocol and all amendments. All patients provided written informed consent before participation in this study.

Patient Population

Eligible patients were outpatients between 18 and 65 years of age who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[20] criteria for bipolar I or II disorder (with or without rapid cycling), current episode depressed, with a duration of at least 4 weeks but less than 1 year, as confirmed by the Structured Clinical Interview for DSM-IV.[21] All patients had a Hamilton Rating Scale for Depression (HAM-D)[22] 17-item score ≥ 20, a HAM-D depressed mood item score ≥ 2, and a Young Mania Rating Scale[23] score ≤ 12 at both the screening and randomization visits.

Patients were not enrolled in the study if they were diagnosed with an Axis I disorder other than bipolar disorder within 6 months prior to screening or if they had a history of nonresponse to an adequate (≥ 6 weeks) trial of more than 2 classes of antidepressants during the current episode. A diagnosis of substance dependence or substance use (except for nicotine) within 12 months prior to screening or a clinically significant medical illness also precluded participation.

Study Medication

Patients were randomly assigned to 1 of 3 groups: quetiapine 600 mg/day, quetiapine 300 mg/day, or placebo. This study used a non–center-specific labeling randomization, stratified by bipolar type (I or II). Treatment randomization was carried out via an interactive voice response system. Quetiapine or placebo was adminis-

tered orally once daily at bedtime in a double-blind manner. Quetiapine was initiated at 50 mg/day and administered to achieve a daily dose of 300 mg/day by day 4 or 600 mg/day by week 1.

Prior and Concomitant Medication

Patients were required to discontinue all psychotropic medications (including benzodiazepines) for at least 5 days before study start. Concomitant treatment with other psychoactive drugs was prohibited, except for low doses of zolpidem tartrate (5–10 mg/day at bedtime for insomnia) and lorazepam (1–3 mg/day for severe anxiety) during the first 3 weeks of treatment, but not during the 8 hours preceding psychiatric assessment.

Efficacy Evaluations

Clinical assessments were conducted at baseline and at weeks 1, 2, 3, 4, 5, 6, 7, and 8. The effect of quetiapine on anxiety symptoms compared with placebo—a secondary objective in the original study design—was assessed using the HAM-A.[24]

Statistical Analyses

The primary and secondary efficacy analyses were performed on the intent-to-treat (ITT) population, which included all randomly assigned patients who took at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment. All analyses were conducted using mixed-effect model repeated-measure (MMRM) methods. Within-patient error was modeled using a banded Toeplitz covariance structure. Least square (LS) mean changes from baseline in total HAM-A score, individual item HAM-A scores, HAM-A psychic anxiety subscale score, HAM-A somatic anxiety subscale score, MADRS inner tension item score, and the HAM-D psychic and somatic anxiety item scores were estimated for the combined quetiapine and placebo groups at each visit using a model with terms for baseline anxiety score, bipolar diagnosis, center, treatment, visit, and treatment-by-visit interaction. Therapeutic effect sizes for the change from baseline in HAM-A total score were calculated by dividing the LS mean difference between each quetiapine dose and placebo or the pooled quetiapine dose group and placebo by the pooled standard deviation. Changes from baseline in total HAM-A score were also estimated for the separate dose groups at each visit.

Analyses were also conducted that included additional terms for either baseline depression severity or the presence of an adverse event of sedation/somnolence, sedation/somnolence-by-treatment interaction, and sedation/somnolence-by-treatment-by-visit interaction. For bipolar I and II subgroup analyses, the bipolar diagnosis term was removed from the model. All analyses were performed using PROC MIXED within the SAS statistical software system (SAS Institute, Inc., Cary, N.C.).

Table 1. Baseline Demographics and Illness Characteristics of Patients With Bipolar Disorder Treated With Quetiapine or Placebo (intent-to-treat)

Characteristic	Quetiapine, 600 mg/d (N = 170)	Quetiapine, 300 mg/d (N = 172)	Placebo (N = 169)
Gender, N (%)			
Male	71 (41.8)	79 (45.9)	64 (37.9)
Female	99 (58.2)	93 (54.1)	105 (62.1)
Age, mean (SD), y	37.3 (11.4)	36.6 (11.2)	38.3 (11.1)
Weight, mean (SD), kg	84.3 (21.9)	87.0 (21.5)	83.8 (21.8)
DSM-IV diagnosis, N (%)			
Bipolar I disorder	114 (67.1)	116 (67.4)	112 (66.3)
Bipolar II disorder	56 (32.9)	56 (32.6)	57 (33.7)
Baseline HAM-A score, mean (SD)	18.7 (7.3)	18.7 (7.3)	18.9 (7.2)
Baseline MADRS score, mean (SD)	30.3 (5.3)	30.3 (5.0)	30.6 (5.3)
Baseline YMRS score, mean (SD)	5.2 (3.0)	5.2 (2.8)	5.1 (3.1)

Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

RESULTS

Patients

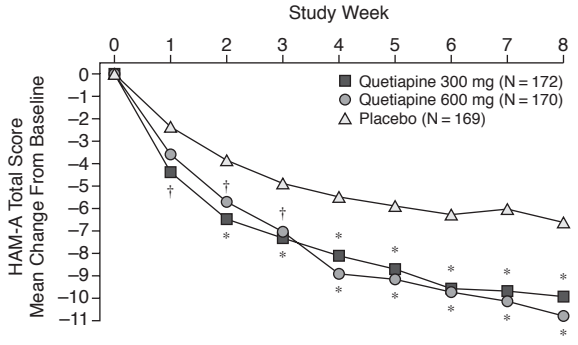
After a total of 838 patients with bipolar I or II disorder presently experiencing an episode of moderate-to-severe depression were screened, 542 fulfilled study criteria and were randomly assigned to receive quetiapine 600 mg/day (N = 180), quetiapine 300 mg/day (N = 181), or placebo (N = 181) for 8 weeks.

Of the 542 patients randomly assigned to treatment, 539 received at least 1 dose of study medication and were included in the safety analysis set. Of these, 511 patients were evaluable (bipolar I: N = 342; bipolar II: N = 169) with data analyzed in ITT efficacy analyses. A total of 326 patients completed the study, with no significant difference in completion rate between the quetiapine groups and placebo: 98 (54.4%) of those treated with quetiapine 600 mg/day, 121 (66.9%) of those treated with quetiapine 300 mg/day, and 107 (59.1%) of those treated with placebo (each active arm nonsignificant when compared with placebo). As shown in Table 1, the 3 groups were well matched with respect to baseline demographic and illness characteristics. Similar mean ± SD HAM-A total scores were observed at baseline for all treatment groups (18.7 ± 7.3, 18.7 ± 7.3, and 18.9 ± 7.2 for quetiapine 600 mg/day, quetiapine 300 mg/day, and placebo, respectively) (Table 1).

Overall Improvement in Anxiety

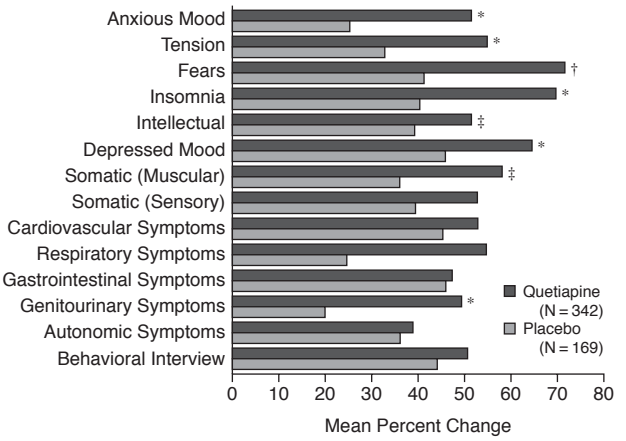
In the overall bipolar population, those treated with quetiapine 300 mg/day had significantly greater improvement in mean HAM-A total score compared with placebo at every assessment, starting with the first evaluation (week 1). In patients treated with quetiapine 600 mg/day,

Figure 1. Mean Change From Baseline in HAM-A Total Score at Each Assessment in Patients With Bipolar Depression Treated With Quetiapine or Placebo (ITT, MMRM)



*p < .001.
†p < .01.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, ITT = intent-to-treat, MMRM = mixed-effect model repeated measure.

Figure 2. Improvement in HAM-A Items From Baseline to Week 8 in Patients With Bipolar Depression Treated With Quetiapine (pooled dose groups) or Placebo (ITT, MMRM)



*p < .001.
†p < .01.
‡p < .05.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, ITT = intent-to-treat, MMRM = mixed-effect model repeated measure.

a significantly greater change in HAM-A total score versus placebo was noted from week 2 onward. The magnitude of effect for both quetiapine groups continued to increase over the 8-week study period. At week 8, the change in HAM-A total score in patients treated with quetiapine 600 mg/day, 300 mg/day, and placebo was –10.8, –9.9, and –6.7, respectively ($p < .001$ for each dose vs. placebo) (Figure 1). The effect sizes for the differences between quetiapine groups and placebo at week 8 were 0.68 for quetiapine 600 mg/day and 0.53 for quetiapine 300 mg/day.

Pooling of Quetiapine Dose Groups

As patients in the quetiapine 600- and 300-mg/day groups did not differ on any baseline demographic or disease characteristics (Table 1), and as both doses showed similar efficacy on the HAM-A total score (Figure 1), all subsequent post hoc analyses on anxiety-related parameters were conducted using the pooled sample of quetiapine dose groups. The pooled analysis (combining the 600- and 300-mg/day dose groups), which included those patients with bipolar I and II disorder, confirmed the significantly greater mean decrease from baseline to endpoint in HAM-A total score in patients treated with quetiapine compared with those treated with placebo (–10.3 vs. –6.7, $p < .001$). The effect size for the difference between quetiapine and placebo at week 8 in the pooled dose group was 0.57.

Improvement in Anxiety Items

Quetiapine demonstrated significant improvements on 8 of the 14 item scores from the HAM-A (Figure 2). Of particular note are the improvements seen with quetiapine in the core HAM-A items of anxious mood and tension. Patients treated with quetiapine showed a significantly greater mean reduction from baseline to endpoint compared with placebo on the HAM-A anxious mood item score (–1.1 vs. –0.5, $p < .001$) and HAM-A tension item score (–1.1 vs. –0.6, $p < .001$). Evaluation of the change in these items over time shows that quetiapine-treated patients demonstrated a significantly greater improvement than placebo-treated patients from early in the study, with the magnitude of effect continuing to increase over the 8-week study period. Quetiapine-treated patients also demonstrated significant improvements as compared with placebo in the following HAM-A scores: depressed mood ($p < .001$), fears ($p = .002$), insomnia ($p < .001$), and intellectual ($p = .025$), somatic (muscular, $p < .05$), and genitourinary ($p < .001$) symptoms.

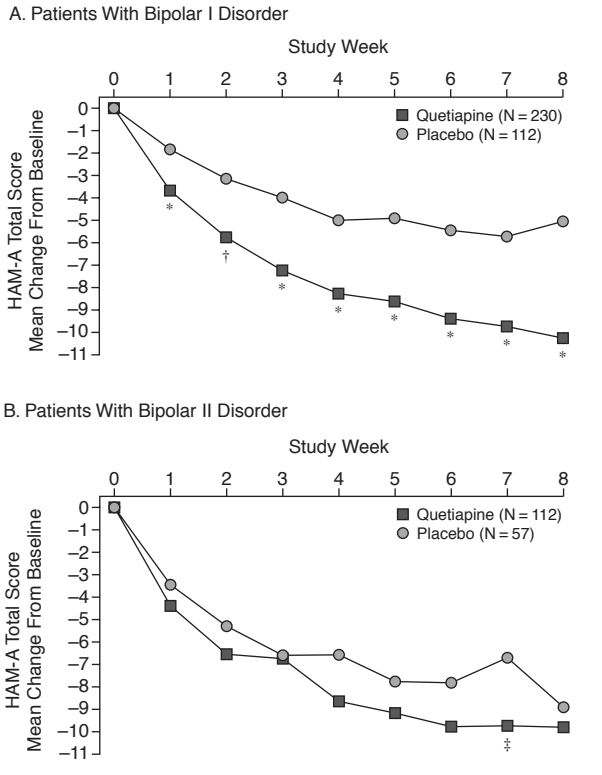
Improvement in Anxiety Subscales

Change from baseline to week 8 in the HAM-A psychic anxiety subscale score was significantly greater with quetiapine versus placebo (–7.5 vs. –4.6, $p < .001$). Treatment-associated change in somatic anxiety subscale score was also significantly greater in quetiapine- versus placebo-treated patients (–2.8 vs. –2.0, $p = .023$).

Anxiety Improvements in Bipolar I and II Subpopulations

To study the anxiolytic effects of quetiapine on the bipolar I and II subpopulations, analyses were performed on the HAM-A total score, the HAM-A anxious mood

Figure 3. Mean Change From Baseline in HAM-A Total Score at Each Assessment in Patients With Bipolar Depression Treated With Quetiapine or Placebo (ITT, MMRM)



*p < .001.
†p ≤ .01.
‡p < .01.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, ITT = intent-to-treat, MMRM = mixed-effect model repeated measure.

and tension items, the HAM-A psychic and somatic anxiety subscales, the MADRS inner tension item, and the HAM-D psychic and somatic anxiety item scores.

Bipolar I. The subset of patients with bipolar I depression treated with quetiapine (pooled dose group) showed significant improvement in overall anxiety symptoms at week 8 compared with placebo as indicated by the change from baseline in HAM-A total score (–10.4 vs. –5.1, p < .001). Figure 3A shows that quetiapine demonstrated significantly greater improvements than placebo at all timepoints from week 1 to week 8 in patients with bipolar I disorder. Patients with bipolar I disorder also showed significantly greater improvements with quetiapine than placebo in the following HAM-A item scores: anxious mood (–1.1 vs. –0.4, p < .001), tension (–1.1 vs. –0.5, p < .001), psychic anxiety subscale (–7.6 vs. –3.6, p < .001), and somatic anxiety subscale (–2.7 vs. –1.4, p < .001).

Significant improvements with quetiapine versus placebo were also seen on the MADRS inner tension item score (–1.6 vs. –0.7, p < .001) and the HAM-D psychic anxiety item score (–1.4 vs. –0.6, p < .001). A similar trend was noted on the HAM-D somatic anxiety item score in patients with bipolar I depression (–0.8 vs. –0.6); however, the difference did not reach statistical significance (p = .053).

Bipolar II. The subset of patients with bipolar II disorder who received quetiapine (pooled dose group) showed improvement comparable to that seen in patients with bipolar I disorder in overall anxiety symptoms as determined by the change from baseline in HAM-A total score at week 8. Despite the clinical improvement seen in the bipolar II population (–9.8) being similar to that seen in the bipolar I group (–10.4), the difference versus placebo for patients with bipolar II disorder was not statistically significant (–9.8 vs. –9.0, p = .473) (Figure 3B).

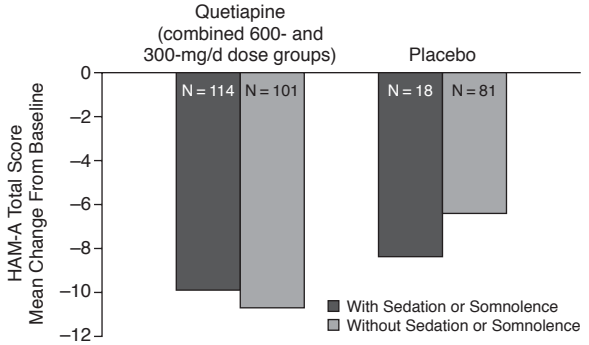
Quetiapine-treated patients with bipolar II disorder showed significantly greater improvements than the placebo-treated group on the HAM-A anxious mood item score (–1.2 vs. –0.7, p = .008) but not on the HAM-A tension item score (–1.0 vs. –0.9, p = .324). In patients with bipolar II disorder, quetiapine reduced the HAM-A psychic anxiety subscale score, but this reduction did not reach statistical significance compared with placebo (–7.0 vs. –6.1, p = .215). However, the change seen in the quetiapine-treated patients with bipolar II disorder was again similar to that seen in the patients with bipolar I disorder (–7.0 and –7.6, respectively), while the placebo response was higher in those patients with bipolar II depression than bipolar I depression (–6.1 and –3.6, respectively). There was no difference between quetiapine and placebo on the HAM-A somatic anxiety subscale score in patients with bipolar II depression (–2.8 vs. –2.9, p = .848). However, the level of improvement seen in the quetiapine groups was again similar to that seen in the bipolar I population.

Patients with bipolar II depression, similar to the bipolar I population, experienced a significantly greater improvement on the MADRS inner tension item score (–1.4 vs. –0.8, p = .007) and the HAM-D psychic anxiety item score (–1.2 vs. –0.7, p = .002) with quetiapine than placebo. No difference was noted between quetiapine and placebo on the HAM-D somatic anxiety item in patients with bipolar II depression (–0.9 vs. –0.8, p = .633).

Concomitant Medication

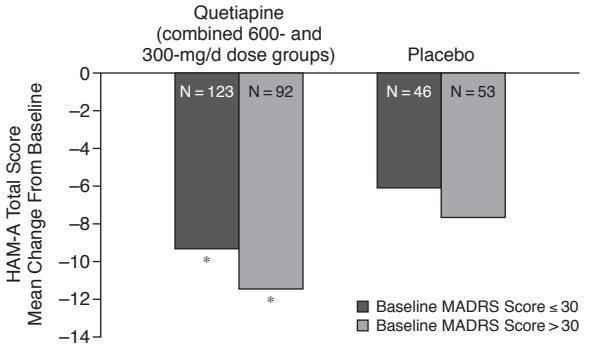
Use of concomitant medication did not differ between treatment groups. Lorazepam was used during the study by 26 patients (7.6%) treated with quetiapine (pooled dose group) and 14 patients (8.3%) treated with placebo. Zolpidem use was also similar among quetiapine- and placebo-treated patients (18 [5.3%] and 13 [7.7%], respectively). The use of concomitant medications was similar for the quetiapine and placebo groups among the bipolar I and II patients.

Figure 4. Improvement in HAM-A Scores From Baseline to Endpoint in Patients Who Did or Did Not Experience Sedation or Somnolence Following Treatment With Quetiapine (pooled dose groups) or Placebo (ITT, MMRM)



Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, ITT = intent-to-treat, MMRM = mixed-effect model repeated measure.

Figure 5. Improvement in Anxiety Levels at Week 8 (change from baseline in HAM-A total score) With Respect to Baseline Severity of Depression (MADRS score) in Patients With Bipolar Depression Receiving Treatment With Quetiapine (pooled dose groups) or Placebo (ITT, MMRM)



*p < .001.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, ITT = intent-to-treat, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed-effect model repeated measure.

Improvement in Anxiety Independent of Sedative Effects

Sedation or somnolence, if they occurred, were generally seen within the first 2 weeks of the study and were predominantly of mild-to-moderate severity. Although sedation or somnolence were generally not severe or persistent, an additional analysis was carried out to determine whether they contributed to the efficacy on anxiety parameters or if the apparent anxiolytic properties of quetiapine were independent of any influence of sedation or somnolence.

The change from baseline to endpoint in HAM-A total score was similar in quetiapine-treated patients (pooled dose group) who experienced sedation or somnolence as compared with those who did not (–9.9 vs. –10.7) (Figure 4). In patients receiving placebo, there was a greater change in HAM-A total score in those with sedation or somnolence compared to those who did not experience sedation or somnolence (Figure 4).

Improvement in Anxiety Levels at Week 8 With Respect to Baseline Severity of Depression

Figure 5 addresses the impact of baseline severity of depression on reduction of anxiety symptoms in the treatment groups. Patients (pooled dose and placebo groups) were divided into 2 groups: those with a baseline MADRS score ≤ 30 and those with a baseline MADRS score > 30. In both groups, quetiapine reduced the HAM-A total score significantly more than placebo ($p < .001$).

DISCUSSION

This secondary analysis from the first large, randomized, double-blind, placebo-controlled study demonstrated that quetiapine was significantly more effective than placebo in the treatment of anxiety symptoms in patients with bipolar depression. Quetiapine showed a significant improvement in anxiety within 1 week of treatment, and this improvement was sustained throughout the study.

The population included in this study allowed the evaluation of the efficacy of quetiapine in treating anxiety associated with either bipolar I or II depression. Quetiapine-treated patients with bipolar I depression experienced significantly greater improvements compared with placebo on the HAM-A total score, the HAM-A anxious mood and tension item scores, the HAM-A psychic and somatic anxiety subscale scores, the MADRS inner tension item score, and the HAM-D psychic anxiety item score. Statistical significance was not reached for the HAM-D somatic anxiety item score. In the bipolar II subset, quetiapine showed significantly greater improvements from baseline compared with placebo on the HAM-A anxious mood item score, the MADRS inner tension item score, and the HAM-D psychic anxiety item score. No significant differences were noted for the HAM-A tension item score, the HAM-A psychic and somatic subscale scores, or the HAM-D somatic anxiety item score. Although the effects of quetiapine to treat anxiety in bipolar II disorder warrant further exploration, these results support the conclusion that quetiapine provides efficacy in the treatment of anxiety in patients with bipolar disorder experiencing a major depressive episode.

The quetiapine-treated patients in the bipolar I and II subgroups responded similarly on the anxiety parameters, including the HAM-A total score change from baseline. However, the placebo group in the bipolar II population

had a higher response rate than in the bipolar I population, which probably contributed to the lack of statistical significance between treatment groups at study endpoint in patients with bipolar II disorder. A high placebo response is not uncommon in studies of bipolar depression.[25] While the mechanism by which patients with bipolar II disorder may be more susceptible to a placebo response is not clear, a recent review of published studies in patients with bipolar disorder has suggested that patients with bipolar II disorder are more likely to exhibit a placebo effect.[26] Further studies into this issue are warranted. Other factors that may impact placebo response should also be considered; for example, patients with higher anxiety levels may show increased placebo response.[27]

Effect size evaluations may assist clinicians in better evaluating the clinical effect of medications and thus in making treatment decisions. An effect size of < 0.4 generally corresponds to a small clinical effect, 0.40 to 0.79 to a moderate effect, and > 0.79 to a large clinical effect.[28] The effect sizes based on the HAM-A total score in this analysis were 0.68 for quetiapine 600 mg/day and 0.53 for quetiapine 300 mg/day, indicating that quetiapine shows a moderate anxiolytic effect in these patients.

As previously reported,[19] quetiapine was well tolerated in this study, with no unexpected adverse events. In those patients who reported sedation or somnolence, it was generally mild to moderate in nature, observed early in treatment (within the first week), and did not generally lead to withdrawal from the study. Improvements in anxiety symptoms with quetiapine were also shown to be independent of any sedative effects of the study treatment, as the improvements observed on HAM-A total score in quetiapine-treated patients were generally comparable in patients with and without sedation or somnolence. Furthermore, it is unlikely that concomitant anxiolytic or sedating medication influenced the findings of this study, as the overall usage of lorazepam and zolpidem (allowed for the first 3 weeks of treatment) was low and did not differ between treatment groups.

Although a previous report has demonstrated that olanzapine (–5.5 vs. –3.5, p = .002) or the combination of olanzapine and fluoxetine (–7.0 vs. –3.5, p < .001) were effective compared with placebo in treating anxiety associated with depression in bipolar disorder,[13] little information is available on the efficacy of atypical antipsychotics in the treatment of comorbid anxiety. In addition, recent evidence[10] suggesting that comorbid anxiety in patients with bipolar disorder is currently inadequately treated in clinical practice emphasizes the importance of this study and the need for future studies to examine the effective treatment of anxiety in bipolar depression.

One limitation of this study is that the improvement in anxiety symptoms may be directly correlated with improvement in depressive symptoms. However, the study was not designed or powered to detect such correlations, and this warrants further study. In addition, the small number of patients in subgroups of patients, such as those with bipolar II disorder or a rapid cycling disease course, does not allow firm conclusions to be drawn on the efficacy of quetiapine treatment in these groups.

In conclusion, although the anxiolytic effects of quetiapine in the subgroup of patients with bipolar II depression warrant further study, this large, randomized, double-blind, placebo-controlled study demonstrates the efficacy of quetiapine to treat anxiety symptoms in patients being treated for bipolar depression.

Drug names: lorazepam (Ativan and others), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbyax), quetiapine (Seroquel), zolpidem (Ambien).

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REFERENCES

1. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537
2. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60:261–269
3. Altshuler LL, Gitlin MJ, Mintz J, et al. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. J Clin Psychiatry 2002;63:807–811
4. Yerevanian BI, Koek RJ, Ramdev S. Anxiety disorders comorbidity in mood disorder subgroups: data from a mood disorders clinic. J Affect Disord 2001;67:167–173
5. Pini S, Cassano GB, Simonini E, et al. Prevalence of anxiety disorders comorbidity in bipolar depression, unipolar depression and dysthymia. J Affect Disord 1997;42:145–153
6. Kessler R. Comorbidity of unipolar and bipolar depression with other psychiatric disorders in a general population survey. In: Tohen M, ed. Comorbidity in Affective Disorders. New York, NY: Marcel Dekker, Inc; 1999:1–25
7. Boylan KR, Bieling PJ, Marriott M, et al. Impact of comorbid anxiety disorders on outcome in a cohort of patients with bipolar disorder. J Clin Psychiatry 2004;65:1106–1113
8. McIntyre R, Katzman M. The role of atypical antipsychotics in bipolar depression and anxiety disorders. Bipolar Disord 2003;5(suppl 2):20–35
9. Fawcett J. Treating impulsivity and anxiety in the suicidal patient. Ann N Y Acad Sci 2001;932:94–102
10. Simon NM, Otto MW, Weiss RD, et al. Pharmacotherapy for bipolar disorder and comorbid conditions: baseline data from STEP-BD. J Clin Psychopharmacol 2004;24:512–520
11. Grunze H. Reevaluating therapies for bipolar depression. J Clin Psychiatry 2005;66(suppl 5):17–25
12. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. JAMA 2004;292:338–343
13. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003;60:1079–1088
14. Cutler AJ. Quetiapine effective in reducing anxiety: clinical evidence. In: New Research Abstracts of the 154th Annual Meeting of the American Psychiatric Association; May 5–10, 2001; Washington, DC. Abstract NR610:165
15. Hamner MB, Deitsch SE, Brodrick PS, et al. Quetiapine treatment in patients with posttraumatic stress disorder: an open trial of adjunctive therapy. J Clin Psychopharmacol 2003;23:15–20
16. Adson DE, Kushner MG, Eiben KM, et al. Preliminary experience with adjunctive quetiapine in patients receiving selective serotonin reuptake inhibitors. Depress Anxiety 2004;19:121–126
17. Atmaca M, Kuloglu M, Tezcan E, et al. Quetiapine augmentation in patients with treatment-resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. Int Clin Psychopharmacol 2002;17:115–119
18. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
19. Calabrese J, Keck P, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005;162:1351–1360
20. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press; 1994
21. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington, DC: American Psychiatric Press, Inc; 1996
22. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
23. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity, and sensitivity. Br J Psychiatry 1978;133:429–435
24. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
25. Keck PE Jr, Welge JA, McElroy SL, et al. Placebo effect in randomized, controlled studies of acute bipolar mania and depression. Biol Psychiatry 2000;47:748–755
26. Vieta E, Carne X. The use of placebo in clinical trials on bipolar disorder: a new approach for an old debate. Psychother Psychosom 2005;74:10–16
27. Shapiro AK, Shapiro E. Patient-provider relationships and the placebo effect. In: Matarazzo JD, Weiss SM, Herd JA, et al, eds. Behavioural Health: A Handbook of Health Enhancement and Disease Prevention. New York, NY: Wiley-Interscience; 1984:371–383
28. Bowden CL, Davis J, Morris D, et al. Effect size of efficacy measures comparing divalproex, lithium and placebo in acute mania. Depress Anxiety 1997;6:26–30