Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression

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Abstract

Background: To evaluate the effectiveness of quetiapine extended release once daily in bipolar depression.

Methods: Double-blind, placebo-controlled study in acutely depressed adults with bipolar I or II disorder, with or without rapid cycling. Patients were randomized to 8 weeks of quetiapine extended release (XR) 300 mg daily monotherapy or placebo. The primary outcome measure was change from baseline to Week 8 in MADRS total score.

Results: Quetiapine XR 300 mg once daily (N = 133) showed significantly greater improvement in depressive symptoms compared with placebo (N = 137) from Week 1 (p < 0.001) through to Week 8 (p < 0.001). Mean change in MADRS total score at Week 8 was -17.4 in the quetiapine XR group and -11.9 in the placebo group (p < 0.001). Response (≥ 50 reduction in MADRS total score) and remission (MADRS total score ≤ 12) rates at Week 8 were significantly higher with quetiapine XR (p < 0.001) compared with placebo (p < 0.05). Quetiapine XR improved core symptoms of depression. The most common adverse events associated with quetiapine XR were dry mouth, somnolence, and sedation. Greater weight gain was observed in patients on quetiapine XR relative to placebo.

Limitations: Fewer patients with bipolar II disorder included, only one fixed dose tested and the lack of an active comparator.

Conclusions: Quetiapine XR (300 mg) once daily monotherapy was significantly more effective than placebo for treating episodes of depression in bipolar I disorder, throughout the 8-week study, with significance observed as early as Day 7. Adverse events were consistent with the known effects of quetiapine.

1. Introduction

Approximately 1.0% of adults are diagnosed with bipolar I disorder at some point in their lifetime. An additional 1.1% are diagnosed with bipolar II disorder (Merikangas et al., 2007). The course of bipolar disorder is lifelong and chronic, with depressive symptoms dominating (Judd et al., 2002, 2003, 2005; Calabrese et al., 2004; Kupka et al., 2007). Despite the availability of varied treatment options, bipolar disorder, and bipolar depression in particular, continues to remain a public health concern (Post, et al., 2003). Even with treatment, bipolar disorder is associated with significant functional and occupational impairment (Kessler et al., 2006; Calabrese et al., 2004; Judd et al., 2005).

A recent study has demonstrated the efficacy of the selective serotonin reuptake inhibitor (SSRI), fluoxetine, in combination with the second-generation antipsychotic, olanzapine, in the treatment of bipolar depression. The olanzapine-fluoxetine combination (OFC) was significantly more efficacious than olanzapine monotherapy, and was associated with higher
response and remission rates, and lower discontinuation rates due to adverse events (Tohen et al., 2003). The need to use more than one medication to manage bipolar disorder—even those medications packaged together as in the case of the OFC—can increase the risk of adverse events and drug-drug interactions. In the study by Tohen and colleagues noted above, patients receiving OFC reported additional side effects than those who received olanzapine monotherapy.

Adverse events may negatively impact patient compliance, which also tends to decrease with increased complexity or inconvenience of the dose regimen (Burton 2005; Fincke et al., 1998; Baldessarini et al., 2008). Well-controlled trials of other novel treatments for bipolar depression have yielded mixed results. Despite established efficacy and Food and Drug Administration (FDA) approval for use in the prevention of new depressive episodes in bipolar disorder, lamotrigine monotherapy has proved relatively ineffective in the treatment of acute bipolar depression (Calabrese et al., 2008). Two double-blind, placebo-controlled trials of aripiprazole for the treatment of bipolar depression in bipolar I patients failed to show significant differences in the change in MADRS score following 8 weeks of treatment (Thase et al., 2008).

The immediate release formulation of quetiapine has been available for the treatment of schizophrenia for several years and is now also indicated for the treatment of bipolar disorder. A once daily extended release (XR) formulation of quetiapine that provides similar 24-hour coverage may represent a useful treatment option for patients with bipolar disorder. The efficacy and safety of the extended release formulation in the treatment of bipolar mania has been demonstrated in another study, the results of which will be published separately (Cutler et al., 2008). Quetiapine XR once-daily is now FDA-approved for the acute treatment of the depressive episodes associated with bipolar disorder, the manic and mixed episodes associated with bipolar I disorder, and the maintenance treatment of bipolar I disorder as adjunctive therapy to lithium or divalproex. This manuscript presents the results from the only study conducted in acute bipolar depression with the quetiapine extended release formulation.

The primary objective of this study was to evaluate the efficacy and safety of quetiapine XR at a dose of 300 mg once daily, compared with placebo, in patients with acute bipolar depression. The 300 mg dose of quetiapine was selected on the basis of previous bipolar depression studies using the IR quetiapine formulation in which quetiapine demonstrated efficacy at 300 mg/day (Calabrese et al., 2005, Thase et al., 2006).

2. Methods

2.1. Study design

This was an 8-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase III study (D144CC00002) conducted in 61 centers in the United States from December 2006 to June 2007. The screening and enrollment phase lasted for up to 35 days and included an initial screening eligibility period (up to 7 days) followed by a washout period (up to 28 days). Following enrollment, eligible patients were randomized in a 1:1 ratio to receive either quetiapine XR 300 mg once daily or placebo for 8 weeks. The study was conducted in accordance with the ethical principles in the Declaration of Helsinki and the International Committee on Harmonisation and signed informed consent was obtained from all patients prior to participation.

2.2. Patient population

Male and female outpatients, between the ages of 18 and 65 years, with a documented clinical diagnosis of bipolar I or II disorder, most recent episode depressed, as defined by DSM-IV criteria (American Psychiatric Association; 2000) were enrolled into this study. Patients with or without a rapid-cycling disease course (rapid cycling defined as ≥ 4 but ≤ 8 episodes of mood disturbance in the previous 12 months) were eligible for participation. To qualify for enrollment, patients were required to have a total score on the 17-item Hamilton Rating Scale for Depression (HAM-D17) of ≥ 20, (Hamilton, 1960), a HAM-D17 Item 1 (depressed mood) score of ≥ 2, and a Young Mania Rating Scale (YMRS) total score of ≤ 12 (Young et al., 1978).

Patients were excluded from the study if they had a DSM-IV diagnosis of another Axis I disorder that was symptomatic or had required treatment 6 months prior to enrollment. Additional exclusion criteria included a history of current substance abuse, a history of nonresponse to an adequate trial (6 weeks) of more than two classes of antidepressants during the current episode of depression, a current episode of depression lasting for more than 12 months or commencing less than 4 weeks prior to enrollment, and clinically significant comorbid disease such as uncontrolled diabetes mellitus, renal or hepatic impairment, or coronary artery disease. Patients were excluded from the study if in the investigator’s judgment they posed a current serious suicidal or homicidal risk, had a HAM-D17 Item 3 score of ≥ 3, or had attempted suicide within the past 6 months. Female patients were excluded if they were nursing, pregnant, or were of childbearing potential and not using a reliable method of birth control.

2.3. Study medication

The quetiapine XR dose was titrated from 50 mg on Day 1 to 100 mg on Day 2, 200 mg on Day 3, and to a maximum of 300 mg on Day 4. From Day 4 to the end of the study, a fixed dose of quetiapine XR 300 mg was administered once daily in the evening.

2.4. Prior and concomitant medications

The use of nonpsychoactive medications, including over-the-counter medications for the treatment of nonpsychiatric concurrent conditions or illnesses was permitted. Concomitant use of psychoactive drugs was restricted, with the exception of the following: lorazepam (up to 2 mg/day) as rescue medication for severe anxiety; zolpidem tartrate (up to 10 mg/day), zaleplon (up to 20 mg/day), zopiclone (up to 7.5 mg/day), or chloral hydrate (up to 1 g/day) for the treatment of insomnia in instances where treatment was ongoing 28 days prior to enrollment; and anticholinergics for the treatment (but not the prevention) of extrapyramidal symptoms (EPS).
2.5. Efficacy evaluations

Clinical assessments of efficacy were conducted at baseline and at weekly intervals thereafter. The primary outcome measure was the change from baseline to Week 8 in Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) total score compared with placebo.

Secondary outcome measures included the change from baseline to Week 8 in MADRS total score in subgroups of patients based on diagnosis (bipolar I or bipolar II disorder) and disease course (with or without rapid-cycling disease); and MADRS individual item scores. Additional secondary outcome measures included the rates of response ($\geq 50\%$ reduction in MADRS total score) and remission (MADRS total score $\leq 12$) at Week 8; Clinical Global Impression-Bipolar-Change (CGI-BP-C) at Week 8; the proportion of patients achieving CGI-BP-C of “much improved” or “very much improved” for overall bipolar illness at Week 8 (Spearing et al., 1997), and the change from baseline to Week 8 in Clinical Global Impression-Bipolar-Severity of Illness (CGI-BP-S) for overall bipolar illness (Spearing et al., 1997).

2.6. Safety and tolerability evaluations

Adverse events (AEs) were classified using the Medical Dictionary for Regulatory Activities (MedDRA) system of nomenclature. Incidences and withdrawals due to AEs and serious adverse events (SAEs) were recorded at each assessment. AEs potentially related to areas of special interest were summarized based on a pool of identified, MedDRA terms for the area of interest; MedDRA preferred AE terms potentially associated with diabetes mellitus included thirst, polyuria, and increase in blood glucose, and EPS-related AEs included akathisia, dystonia, extrapyramidal disorder, hypertonia, and tremor. In addition, all patients were evaluated for EPS changes according to the change in Simpson Angus Scale (SAS) (Simpson and Angus, 1970) and Barnes Akathisia Rating Scale (BARS) (Barnes 1989) scores from baseline to Week 8. The incidence of treatment-emergent mania was assessed using the YMRS (YMRS total score $\geq 16$ on two consecutive assessments or at final assessment) or an AE report of treatment-emergent mania or hypomania. The incidence of suicidality was evaluated using a classification similar to the Columbia Classification criteria to determine estimates of relative risk in the two treatment groups.

Columbia Classification codes 1 to 4 (suicide or potential suicide events with suicidal intent determined) were used to indicate suicidal behavior or ideation. Potential suicide events also included Columbia codes 5, 6, or 9 (possible suicidal ideation/behavior). Changes from baseline were recorded for clinical laboratory parameters, electrocardiograms, vital signs, and weight. Patients were requested to fast for 8 hours before samples were drawn. Over 85% of all laboratory samples were collected in a fasting state based on reported last meal by the patient; a separate analysis was not performed for those samples reported to be fasting data. Mean changes in serum glucose levels were also evaluated on the basis of presence or absence of potential risk factors for diabetes, which included fasting glucose levels $\geq 5.5$ and $< 6.93$ mmol/L ($\geq 100$ and $< 126$ mg/dL) at randomization, a history of diabetes or obesity, or body mass index (BMI) $\geq 35$ kg/m$^2$.

2.7. Statistical analysis

Efficacy analyses were based on the modified intent-to-treat (MITT) population, which included all randomized patients who received at least one dose of study medication and who had a baseline and at least one postbaseline MADRS assessment. All efficacy outcomes were analyzed using analysis of covariance (ANCOVA) and last observation carried forward (LOCF) methodology.

Dichotomous variables including responders and remitters were analyzed using a Cochran-Mantel-Haenszel (CMH) test and logistical model. The effect size was calculated by dividing the least squares (LS) mean difference between quetiapine and placebo with the estimated pooled standard deviation estimated in a Mixed Model Repeated Measurement (MMRM) analysis. Statistical analysis of patient subgroups was estimated using the MMRM approach. All statistical tests were two-sided with a significance level of 5%. Confidence intervals (CI) of 95% are presented, where appropriate.

The safety population included all patients who took at least one dose of study medication. Safety analyses were based on descriptive statistics, and the suicidality analysis was based on the Columbia classification system outlined above.

This study was powered at 90% for a two-sided test at $\alpha = 0.05$ for the comparison between quetiapine XR and placebo using a 4-unit change from baseline in MADRS total score from placebo with a pooled standard deviation of 10. A 1:1 randomization yielded the planned sample size of 140 for each treatment group.

3. Results

3.1. Patients and disposition

A total of 418 patients were screened, and 280 patients were randomized to receive quetiapine XR 300 mg once daily ($N=140$) or placebo ($N=140$). A total of 277 patients were included in the safety population and of these, 270 were included in the MITT population subset (133 patients were randomized to treatment with quetiapine XR 300 mg once daily and 137 received placebo). Study completion rates were comparable between treatment groups: 62.1% for the quetiapine XR 300 mg once daily group and 68.6% for the placebo group. The disposition of patients enrolled in this study is illustrated in Fig. 1.

Treatment groups were comparable with respect to disease and demographic characteristics at baseline (Table 1). The number of women ($N=174$) enrolled into the study was almost twice that of men ($N=96$).

3.2. Efficacy variables

3.2.1. MADRS total score

A significantly greater reduction in MADRS total score was observed among patients treated with quetiapine XR 300 mg once daily compared with placebo after 1 week of treatment. This improvement was observed consistently until the last assessment at Week 8 ($p<0.001$ vs placebo at all assessments; Fig. 2). The mean changes in MADRS total score as assessed by LOCF analysis from baseline to Week 8 were -17.4 and -11.9 in the quetiapine XR 300 mg once daily and placebo.
groups, respectively (p < 0.001). The effect size (MMRM) for quetiapine XR at Week 8 was 0.61.

Significantly greater improvements in MADRS total score were associated with quetiapine XR 300 mg once daily compared with placebo in subgroups of patients with bipolar I and II disorder (Fig. 3a). For patients with bipolar I disorder, the mean changes in MADRS total score from baseline to Week 8, as assessed by MMRM analysis, were -20.1 and -14.9 for quetiapine XR 300 mg once daily and placebo, respectively (p < 0.001). The corresponding changes for patients with bipolar II disorder were -18.4 and -15.1, respectively (p < 0.05). The effect size (MMRM) for patients with bipolar I disorder was 0.64 and for those with bipolar II disorder 0.45.

Quetiapine XR 300 mg once daily was significantly more effective (p < 0.01) than placebo in patients with and without a rapid cycling disease course (Fig. 3b).

Quetiapine XR 300 mg once daily was associated with significantly greater improvement (p < 0.05) in 8 of the 10 individual MADRS item scores at Week 8 compared with placebo (LOCF analysis) (Fig. 4).

A significantly greater proportion of patients in the quetiapine XR 300 mg once daily group responded to treatment compared with the placebo group, as evidenced by a ≥ 50% reduction in MADRS total score. Response was apparent from Week 2 through to the last assessment at Week 8 (p < 0.01 at Weeks 2 and 3 and p < 0.001 at all time points thereafter). At Week 8, 65.4% of patients in the quetiapine XR 300 mg once daily group had responded to treatment, compared with 43.1% of the placebo group (p < 0.001; Fig. 5). The proportion of patients achieving remission, defined as a MADRS total score ≤ 12, was significantly greater in the quetiapine XR 300 mg once daily group compared with the placebo group from Week 1 onward, with this improvement again sustained to Week 8 (p < 0.05 at all time points). At Week 8, the proportion of remitters was 54.1% in the quetiapine XR 300 mg once daily group versus 39.4% in the placebo group (p = 0.018; Fig. 5). A

*Two patients were randomized to quetiapine XR but were treated with placebo and were reclassified to the placebo group for the safety analysis.

ITT = intent-to-treat.
post hoc analysis looking at various definitions of euthymia with a criterion of MADRS ≤ 8 and YMRS ≤ 12 indicated that significantly more patients in the quetiapine XR group (40.6%) were “euthymic” as compared with patients in the placebo group (28.5%; p = 0.04).

3.2.2. CGI-BP-Severity of Illness and Change (Overall Bipolar Illness)

At Week 8, the improvement in CGI-BP-S score was significantly greater in the quetiapine XR 300 mg once daily group than in the placebo group (-1.8 vs -1.2, respectively; p < 0.001). A significantly higher proportion of patients in the quetiapine XR 300 mg once daily treatment group had a CGI-BP-C score of “much improved” or “very much improved” than the placebo group. This trend commenced during the first week of treatment and continued up to Week 8 (p < 0.05 for all time points). At Week 8, 63.2% and 39.4% of the patients in the quetiapine XR 300 mg once daily and placebo groups, respectively, had CGI-BP-C scores of “much improved” or “very much improved” (p < 0.001).

3.3. Safety and tolerability

Overall, AEs were reported by 88.3% (121/137) of patients in the quetiapine XR treatment group and 68.6% (96/140) of the placebo group. The proportion of patients withdrawing from the study due to AEs was also higher in the quetiapine XR group (12.14% [17/140] vs 7.2% [2/140], respectively; Fig. 1; note that events related to worsening of underlying depression are categorized separately). The most common AEs to prompt discontinuation of treatment with quetiapine XR 300 mg once daily were sedation (6.6%) and somnolence (3.6%). No patients treated with placebo discontinued treatment as a result of these AEs. Overall, the most commonly reported AEs included dry mouth (37.2%), somnolence (29.2%), sedation (23.4%), dizziness (13.1%), and increased appetite (12.4%) in the quetiapine XR 300 mg group; and in the placebo group, dizziness (10.7%), headache (10.0%), dry mouth (7.1%), sedation (7.1%), and nausea (7.1%) (Table 2). Most AEs were mild-to-moderate in intensity. The incidence of SAEs was similar between treatment groups (1.5% and 1.4%, respectively) and no deaths were reported during the study.

3.3.1. Extrapyramidal symptoms

AEs potentially associated with EPS (including akathisia, dystonia, extrapyramidal disorder, hypertonia, and tremor) were reported at frequencies of 4.4% in the quetiapine XR group compared with 0.7% in the placebo group. The concomitant use of anticholinergic medication was low (<1%) and similar between treatment groups. The majority of patients in both treatment groups showed “no change” in SAS and BARs scores over the course of treatment (75.0% and 78.8% [SAS] and 79.3% and 87.1% [BARS] for quetiapine XR and placebo, respectively). Additionally, 18.1% and 16.4% patients in the quetiapine XR group and 16.7% and 11.4% patients in the placebo group showed “improvement” in SAS and BARS scores, respectively.

3.3.2. Treatment-emergent mania

No AEs associated with mania or hypomania were reported in either treatment group. At Week 8, the proportion of patients with YMRS-defined treatment-emergent mania or

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**Table 1**
Baseline demographic and disease characteristics of the patients treated with quetiapine XR 300 mg once daily or placebo (MITT population).

<table>
<thead>
<tr>
<th></th>
<th>Quetiapine XR 300 mg once daily N=133</th>
<th>Placebo N=137</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (33.8)</td>
<td>51 (37.2)</td>
</tr>
<tr>
<td>Female</td>
<td>88 (62.6)</td>
<td>86 (62.8)</td>
</tr>
<tr>
<td>Mean age (years), mean (SD)</td>
<td>39.0 (11.3)</td>
<td>39.9 (12.8)</td>
</tr>
<tr>
<td>Mean weight (kg), mean (SD)</td>
<td>88.7 (22.1)</td>
<td>88.9 (22.7)</td>
</tr>
<tr>
<td>DSM-IV diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar I disorder</td>
<td>107 (80.5)</td>
<td>110 (80.3)</td>
</tr>
<tr>
<td>Bipolar II disorder</td>
<td>26 (19.5)</td>
<td>27 (19.5)</td>
</tr>
<tr>
<td>Rapid cycling, n (%)</td>
<td>36 (27.1)</td>
<td>38 (27.7)</td>
</tr>
<tr>
<td>MADRS total score, mean (SD)</td>
<td>29.8 (5.2)</td>
<td>30.1 (5.5)</td>
</tr>
<tr>
<td>HAM-D_17 total score, mean (SD)</td>
<td>24.8 (3.5)</td>
<td>24.6 (3.3)</td>
</tr>
<tr>
<td>CGI-BP overall bipolar illness score, mean (SD)</td>
<td>4.5 (0.6)</td>
<td>4.4 (0.7)</td>
</tr>
</tbody>
</table>

MITT = modified intent-to-treat; CGI-BP = Clinical Global Impression-Bipolar; HAM-D_17 = 17-item Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale.

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**Fig. 2.** Mean change from baseline in MADRS total score over time in patients with bipolar disorder (MITT, LOCF).

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hypomania (YMRS score \( \geq 16 \) on two consecutive assessments or at final assessment) was lower in the quetiapine XR group (4.4%) than in the placebo group (6.4%).

### 3.3.3. Suicidality

The Columbia analysis showed the number of patients with suicidal behavior or ideation to be low and comparable

![Graphs showing percentage improvement in MADRS individual item scores from baseline at Week 8 in patients with bipolar disorder (MITT, LOCF).]
across treatment groups. One patient (0.7%) in the quetiapine XR group and two patients (1.4%) in the placebo group exhibited suicidal behavior or ideation with intent (Columbia codes 1, 2, 3 or 4). Additionally, four patients (2.9%) in the quetiapine XR group showed possible suicidal behavior or ideation (Columbia codes 5, 6, or 9).

3.3.4. Weight change

After 8 weeks, the mean weight gain (LOCF) in the quetiapine XR 300 mg once daily group was greater than that in the placebo group (+1.3 kg vs –0.2 kg, respectively). Weight gain associated with quetiapine XR was generally consistent across baseline BMI categories, with the exception of the <18.5 and ≥40 kg/m² categories in which quetiapine XR 300 mg once daily was associated with weight loss (mean change: −0.9 kg [n = 1] and −0.5 kg [n = 18] for <18.5 and ≥40 kg/m² categories, respectively). A higher proportion of patients treated with quetiapine XR showed weight gain ≥7% compared with those in the placebo group (8.2% vs 0.8%, respectively; Table 3). When categorized by baseline BMI, weight changes were not consistent over BMI categories in terms of direction of change and numbers reaching the 7% threshold, but the number of patients in each BMI category were insufficient to reach any conclusions. There were no patients who met the criteria of 15% or 25% weight gain from baseline.

3.3.5. Changes in laboratory and metabolic parameters

Following 8 weeks of treatment, the mean change from baseline in serum glucose levels in the overall safety population was similar between treatment groups (Table 3). However, by individual patient, the shift in fasting glucose levels to clinically important high values (≥7 mmol/L) at Week 8 was greater in the quetiapine XR 300 mg once daily group (5.8%) than in the placebo group (2.1%).

Among patients with diabetic risk factors, the mean change in serum glucose levels was higher in the quetiapine XR 300 mg once-daily group compared with the placebo group (Table 3). Conversely, in patients without diabetic risk factors, the mean change was lower in the quetiapine XR group.

Mean changes in total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL cholesterol) were similar in both treatment groups (Table 3). Patients in the quetiapine XR group showed a slight increase in mean triglyceride levels versus a slight decrease in the placebo group. For total cholesterol, a greater proportion of patients in the quetiapine XR group (7.1%) than in the placebo group (2.8%), showed a shift to clinically important values (≥6.21 mmol/L) at Week 8. For triglycerides, the proportion of patients with a shift to a clinically important value (≥2.26 mmol/L) at Week 8 was similar between treatment groups (8.3% and 7.5%, respectively).

4. Discussion

This is the first randomized, parallel-group, placebo-controlled study to evaluate the efficacy and safety of the extended release formulation of quetiapine in bipolar depression. Quetiapine extended release monotherapy at a dose of 300 mg once daily was significantly more effective than placebo.
in the treatment of acute episodes of bipolar depression, both in the primary and several secondary outcome measures. The rapidity of effect associated with quetiapine XR is notable given the treatment duration of quetiapine in bipolar depression (Calabrese et al., 2005, Thase et al., 2006), in this study, treatment with quetiapine XR 300 mg once daily was not associated with treatment-emergent mania or hypomania.

Patients treated with quetiapine XR 300 mg once daily reported higher weight gain than those treated with placebo; though none of the patients reported withdrawing from treatment as a direct result. Mean changes in serum glucose levels from baseline to study end were similar between treatment groups. However, higher mean changes in HbA1c, triglycerides, and insulin were noted in the quetiapine XR treatment group compared with the placebo group.

Further prespecified secondary safety analyses were carried out in a subgroup of patients defined as potentially at higher risk for changes in metabolic parameters. This subgroup was identified by fasting glucose levels \( \geq 5.5 \text{ mmol/L} \) and \( <6.93 \text{ mmol/L} \) at randomization (patients required to have fasted for 8 hours prior to blood draws therefore fasting status is presumed but not confirmed) b) history of diabetes or obesity or, c) BMI \( \geq 35 \text{ kg/m}^2 \).

The consistent effectiveness of quetiapine in bipolar depression may be attributable to its putative mechanism of action. It has been postulated that one of the potential antidepressant mechanisms exhibited by quetiapine is the competitive inhibition of norepinephrine reuptake by norquetiapine, an active quetiapine metabolite that exhibits a high affinity for the norepinephrine transporter (NET) (Goldstein et al., 2007).

The incidence of AEs observed in this study following treatment with quetiapine extended release was consistent with the known tolerability profile of quetiapine in bipolar depression (Calabrese et al., 2005, Thase et al., 2006). The incidence of AEs potentially associated with EPS was higher following treatment with quetiapine XR 300 mg once daily than with placebo, though use of anticholinergic medications was similar and the majority of patients showed no change in SAS or BARS scores. This is similar to a study of quetiapine XR in bipolar mania (Cutler et al., 2008).

A significant drawback associated with the use of antidepressant medication in the treatment of bipolar disorder is the risk of switching to mania or hypomania (Leverich et al., 2006). Consistent with the known profile of quetiapine in bipolar depression (Calabrese et al., 2005, Thase et al., 2006), in this study, treatment with quetiapine XR 300 mg once daily was not associated with treatment-emergent mania or hypomania.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Quetiapine XR 300 mg once daily N = 137</th>
<th>Placebo N = 140</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change (kg), mean (SD)</td>
<td>N Mean (SD)</td>
<td>N Mean (SD)</td>
</tr>
<tr>
<td>Weight change ≥7% (n, %)</td>
<td>9 8.2</td>
<td>1 0.8</td>
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<tr>
<td>Parameter</td>
<td>N Mean change (SD)</td>
<td>N Mean change (SD)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>103 0.34 (0.99)</td>
<td>113 0.33 (0.89)</td>
</tr>
<tr>
<td>Glucose (patients with diabetic risk factors) (mmol/L)*</td>
<td>48 0.44 (0.85)</td>
<td>57 0.31 (1.05)</td>
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<tr>
<td>Glucose (patients without diabetic risk factors) (mmol/L)</td>
<td>50 0.24 (1.03)</td>
<td>55 0.33 (0.66)</td>
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<tr>
<td>HbA1c</td>
<td>104 0.08 (0.24)</td>
<td>121 0.10 (0.24)</td>
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<tr>
<td>HbA1c (patients with diabetic risk factors)</td>
<td>50 0.12 (0.23)</td>
<td>58 0.02 (0.23)</td>
</tr>
<tr>
<td>HbA1c (patients without diabetic risk factors)</td>
<td>50 0.07 (0.19)</td>
<td>57 0.01 (0.23)</td>
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<tr>
<td>Insulin (mmol/L)</td>
<td>101 56.66 (212.58)</td>
<td>115 29.49 (95.25)</td>
</tr>
<tr>
<td>Insulin (patients with diabetic risk factors) (pmol/L)</td>
<td>49 67.73 (275.57)</td>
<td>57 31.82 (120.26)</td>
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<tr>
<td>Insulin (patients without diabetic risk factors) (pmol/L)</td>
<td>47 46.28 (134.91)</td>
<td>53 28.58 (65.09)</td>
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<tr>
<td>Total cholesterol (mmol/L)</td>
<td>103 −0.09 (0.79)</td>
<td>121 −0.13 (0.66)</td>
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<tr>
<td>LDL cholesterol, Friedwald assessment (mmol/L)</td>
<td>97 −0.12 (0.63)</td>
<td>114 −0.13 (0.57)</td>
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<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>103 0.01 (0.24)</td>
<td>121 0.01 (0.27)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>103 0.18 (2.25)</td>
<td>121 −0.03 (1.29)</td>
</tr>
</tbody>
</table>

HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; *Diabetic risk factors defined as: a) Fasting glucose \( \geq 5.5 \text{ mmol/L} \) and \( <6.93 \text{ mmol/L} \) at randomization (patients required to have fasted for 8 hours prior to blood draws therefore fasting status is presumed but not confirmed) b) history of diabetes or obesity or, c) BMI \( \geq 35 \text{ kg/m}^2 \).
as smaller snacks or beverages. However, these results are generally consistent with two long-term studies that evaluated the maintenance effect of quetiapine, in combination with lithium or divalproex, in which the incidence density of a single emergent fasting blood glucose value ≥6.93 mmol/L (≥126 mg/dL) was higher in the quetiapine group compared with placebo (Vieta et al., 2008; Suppes et al., 2009).

This study had a number of methodological limitations. A majority of patients (approximately 80%) enrolled in this study were patients with bipolar I disorder thereby limiting the availability of information about patients with bipolar II disorder. Although quetiapine XR 300 mg once daily was not associated with an increased risk of suicidality, the exclusion of patients with a current suicidal or homicidal risk limits the generalizability of these findings.

While doses of 300 and 600 mg once daily of quetiapine IR have been shown to be effective for treatment of bipolar depression, only a fixed dose of 300 mg once daily was evaluated in this study. This is the lowest dose studied for this indication and the recommended dose of quetiapine for the treatment of bipolar depression. Further study will be needed to assess the potential efficacy of lower doses for treatment of acute bipolar depression.

Another limiting factor of this study was the absence of an active comparator. Finally, while metabolic parameters were examined more thoroughly in this study relative to other studies with second generation antipsychotics, results should be interpreted along with the limitations inherent in outpatient studies, specifically uncertain fasting status and variable time of day for collecting blood and patient weights.

5. Conclusions

The results of this trial demonstrate that quetiapine XR 300 mg once daily monotherapy is an effective treatment for acute bipolar depression. Significant improvement in symptoms were seen after 1 week of treatment and continued throughout the 8 week study. Quetiapine XR 300 mg once daily was equally effective in patients with bipolar I and II disorder and rapid or nonrapid cycling, although efficacy in bipolar II disorder and the rapid or nonrapid cycling subpopulations require further confirmation in future studies due to the smaller number of patients in these subpopulations in this study. Treatment with quetiapine XR 300 mg once daily monotherapy was overall well tolerated. Additional studies on this new formulation may lead to further understanding of its effects on adherence and patient acceptability.

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Conflict of interest

Disclosures: Dr. Suppes has received funding or medications for clinical studies in the last 12 months from: Abbott, AstraZeneca, GlaxoSmithKline, JDS, National Institute of Mental Health, Novartis, Pfizer, and The Stanley Medical Research Institute. Dr. Suppes has had a advisory board with Orexigen and no speaking bureau activity within the last 12 months and has no conflicting financial interests or stock ownership. Royalties are received from Compact Clinical Publishers.

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