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

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Abstract

Objectives: To evaluate the effectiveness of extended-release quetiapine fumarate (quetiapine XR) as once-daily monotherapy for bipolar depression.

Methods: Patients in this double-blind, placebo-controlled study were acutely depressed adults with bipolar I or II disorder (with or without rapid cycling), and were randomized to 8 weeks of once-daily treatment with quetiapine XR 300 mg (n=133) or placebo (n=137). The primary outcome measure was change from baseline to endpoint (Week 8) in MADRS total score. Secondary outcome measures included response (MADRS total score reduction ≥50%) and remission (MADRS total score ≤12) rates at endpoint, changes from baseline to endpoint in MADRS item scores, and CGI-BP severity of illness and change. Change from baseline was compared between groups with analysis of covariance using LOCF.

Results: Quetiapine XR 300 mg qd was significantly more effective than placebo in improving depressive symptoms, from first assessment (Week 1; *P*<0.001) to endpoint (*P*<0.001). Compared with placebo, quetiapine XR was associated with higher response (*P*<0.001) and remission (*P*<0.05) rates and greater improvements from baseline to endpoint in MADRS total score (-17.43 vs -11.92; *P*<0.001), MADRS item scores for core symptoms of depression, and CGI-BP-related outcomes at Week 8. Most common AEs with quetiapine XR were dry mouth, somnolence, and sedation.

Conclusions: Quetiapine XR (300 mg) once-daily monotherapy was efficacious (from Weeks 1 through 8) compared with placebo and generally well tolerated in bipolar depression.

Introduction

- The lifetime prevalence of bipolar disorder in the United States is estimated to be between 1 and 3.7%[1,2]
- Both the simplicity of monotherapy and ease of needing only 1 medication for antidepressant and antimanic benefit might be expected to enhance treatment compliance
- Quetiapine is the only antipsychotic that has been approved as monotherapy to treat both acute mania and depression associated with bipolar disorder[3]
- Quetiapine IR monotherapy is effective in treating acute mania and depression episodes in patients with bipolar disorder, and a qd XR formulation may offer enhanced patient compliance

Objective

- To evaluate the efficacy and tolerability of quetiapine XR 300 mg qd monotherapy in the treatment of patients with bipolar disorder experiencing acute episodes of depression

Methods

Study design

- This was an 8-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase III study (D144CC00002) conducted in the United States

Study population

- Male or female outpatients aged 18 to 65 years with a clinical diagnosis of bipolar I or bipolar II disorder, most recent episode depression, with or without a rapid cycling disease course (≥4 episodes of mood disturbance but ≤8 episodes in the previous 12 months) as defined by DSM-IV were enrolled in this study
- Patients were required to meet the following criteria at enrollment and at randomization:
  - HAM-D_{17} total score ≥20
  - HAM-D_{17} Item 1 (depressed mood) score ≥2
  - YMRS total score ≤12
- Patients with a DSM-IV diagnosis of an Axis I disorder other than bipolar disorder or with a history of substance abuse were excluded from the study

Study treatment

- Following an enrollment and washout phase of up to 35 days, patients were randomly allocated 1:1 to either quetiapine XR 300 mg qd or placebo for 8 weeks
- Quetiapine XR was initiated at 50 mg on Day 1, increased to 100 mg on Day 2, and 200 mg on Day 3 in order to reach a maximum dose of 300 mg by Day 4. From Day 4 to the end of the study, a fixed dose of quetiapine XR 300 mg qd was administered in the evening
- Concomitant use of psychoactive drugs was prohibited except for lorazepam (up to 2 mg qd) as rescue medication for severe anxiety; zolpidem tartrate (up to 10 mg qd), zaleplon (up to 20 mg qd), zopiclone (up to 7.5 mg qd) or chloral hydrate (up to 1 g/d) to treat insomnia; and anticholinergics to treat EPS

Efficacy analyses

Primary outcome measure

- Change from baseline to Week 8 in MADRS total score compared with placebo

Secondary outcome measures

- Change from baseline to Week 8 in:
  - MADRS total score in subgroups of patients with bipolar I or bipolar II disorder
  - MADRS total score in subgroups of patients with and without a rapid cycling disease course
  - MADRS individual item scores
- Rates of response, defined as ≥50% reduction in MADRS total score, and remission, defined as a MADRS total score ≤12, at Week 8
- CGI-BP-C at Week 8 and proportion of patients achieving CGI-BP-C of "much improved" or "very much improved" for overall bipolar illness at Week 8
- Change from baseline to Week 8 in CGI-BP-S for overall bipolar illness

Safety analyses

- Incidence of and withdrawals due to AEs, and proportion of patients with SAEs
- EPS, including akathisia, as measured by the change from baseline to Week 8 in SAS and BARS scores
- Proportion of patients with treatment-emergent mania/hypomania (defined as YMRS total score ≥16 on 2 consecutive assessments or at final assessment or an AE report of treatment-emergent mania or hypomania)
- Incidence of suicidality, evaluated using a classification similar to the Columbia Classification criteria in the 2 treatment groups. Columbia Classification codes 1 to 4 were used to indicate suicidal behavior/ideation
- Change from baseline in laboratory values, vital signs, and weight

Statistical analyses

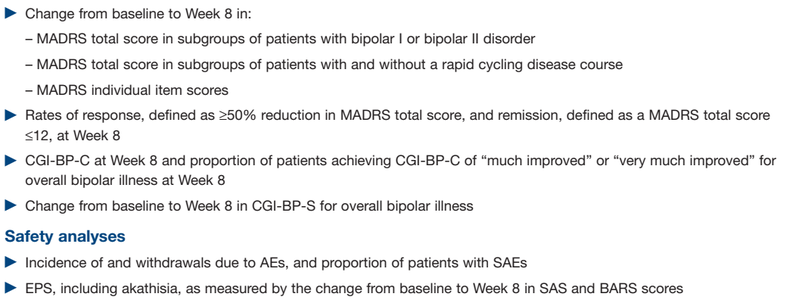
- The ITT population, which included all randomized patients who received at least 1 dose of study treatment, was assessed for all efficacy outcome measures, using ANCOVA and LOCF methodology
- Dichotomous variables, including the proportion of patients who met response and remission criteria were analyzed using a Cochran-Mantel-Haenszel test
- The effect size was calculated as the LS mean difference between quetiapine and placebo divided by the estimated pooled SD estimated in a MMRM analysis. The LS mean change from baseline was defined as the change from baseline adjusted for the baseline level
- All statistical tests were 2-sided with a significance level of 5%. Where appropriate, 95% confidence intervals are presented
- Descriptive statistics are presented for all safety analyses

Results

Baseline demographics and disease characteristics

- A total of 418 patients were screened and 280 patients were randomized to receive:
  - Quetiapine XR 300 mg qd (n=140)
  - Placebo (n=140)
- The safety population consisted of 277 patients who had received at least 1 dose of study medication and the ITT population comprised 270 patients (**Figure 1**)

Figure 1. Study design (ITT population)



- Study completion rates were similar in both treatment groups: 62.1% in the quetiapine XR 300 mg qd group and 68.6% in the placebo group
- In both treatment groups, at least 98% of patients were classified as compliant, as determined by returned tablet counts and defined as ≥70% consumption of doses. However, it should be noted that this percentage may be an overestimate as patients who did not return their medication were considered as having taken full medication dose
- Both treatment groups were well balanced with respect to baseline demographics and disease characteristics (**Table 1**)

Improvement in MADRS total score

- Quetiapine XR 300 mg qd was significantly more effective than placebo in reducing the MADRS total scores from Week 1 onward, and this improvement was sustained until the last assessment at Week 8 (*P*<0.001 vs placebo at all time points; **Figure 2**)
- The mean change in MADRS total score from baseline to Week 8 was -17.4 in the quetiapine XR 300 mg qd group versus -11.9 in the placebo group (*P*<0.001)

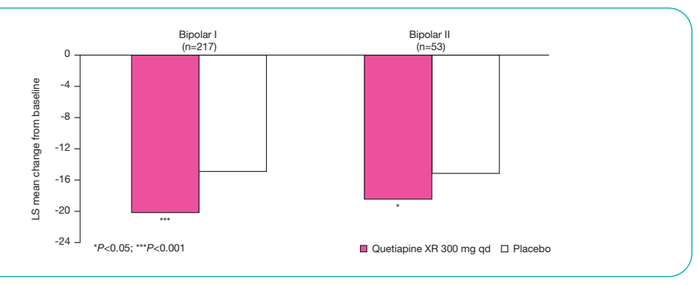
Table 1. Baseline demographics and disease characteristics (ITT population)

	Quetiapine XR 300 mg qd (n=133)	Placebo (n=137)
Gender, n (%)		
Male	45 (33.8)	51 (37.2)
Female	88 (66.2)	86 (62.8)
Mean age (y), mean (SD)	39.0 (11.3)	39.9 (12.8)
Mean weight (kg), mean (SD)	88.7 (22.1)	88.9 (22.7)
DSM-IV diagnosis, n (%)		
Bipolar I disorder	107 (80.5)	110 (80.3)
Bipolar II disorder	26 (19.5)	27 (19.7)
Rapid cycling, n (%)	36 (27.1)	38 (27.7)
MADRS score, mean (SD)	29.8 (5.2)	30.1 (5.5)
HAM-D_{17} score, mean (SD)	24.8 (3.5)	24.6 (3.3)
CGI-BP overall bipolar illness score, mean (SD)	4.5 (0.6)	4.4 (0.7)

Figure 2. Mean change from baseline in MADRS total score (ITT, LOCF)

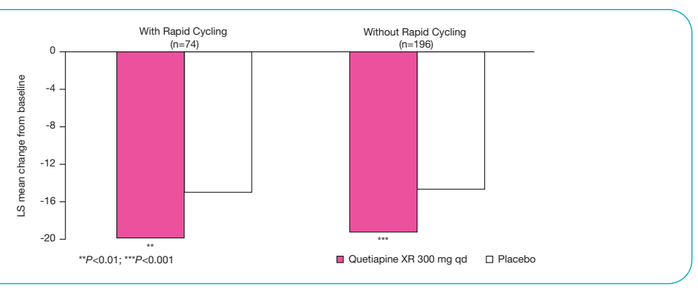
- Patients with both bipolar I and II disorder treated with quetiapine XR 300 mg qd showed significantly greater improvements (*P*<0.001 for bipolar I; *P*<0.05 for bipolar II; MMRM) in MADRS total score at Week 8 when compared with patients in the placebo group; statistical analysis of subgroup data was limited to the MMRM approach
  - Mean change in MADRS total score from baseline at Week 8 for patients with bipolar I disorder was -20.1 and -14.9 with quetiapine XR 300 mg qd and placebo, respectively, and for patients with bipolar II disorder was -18.4 and -15.1 (**Figure 3**) (baseline scores were: 30.2 for quetiapine XR 300 mg qd and 30.1 for placebo in patients with bipolar I and 28.1 and 30.3, respectively, in patients with bipolar II)

Figure 3. Mean change in MADRS total score in patients with bipolar I and bipolar II disorder at Week 8 (observed cases [OC], MMRM)



- At Week 8 there were significantly greater improvements in the MADRS total score observed in both patients with (*P*<0.01) and without (*P*<0.001) a rapid cycling disease course treated with quetiapine XR 300 mg qd compared with those treated with placebo
  - The mean change from baseline to Week 8 in the MADRS total score was -19.2 with quetiapine XR 300 mg qd versus -14.6 with placebo in patients with a rapid cycling disease course (mean baseline MADRS total score: quetiapine XR 300 mg qd 29.5; placebo 30.6). In patients without a rapid cycling disease course, the mean change from baseline at Week 8 in MADRS total score was -19.8 and -15.0 with quetiapine XR 300 mg qd and placebo, respectively (mean baseline MADRS total score: quetiapine XR 300 mg qd 29.9; placebo 30.0) (**Figure 4**)

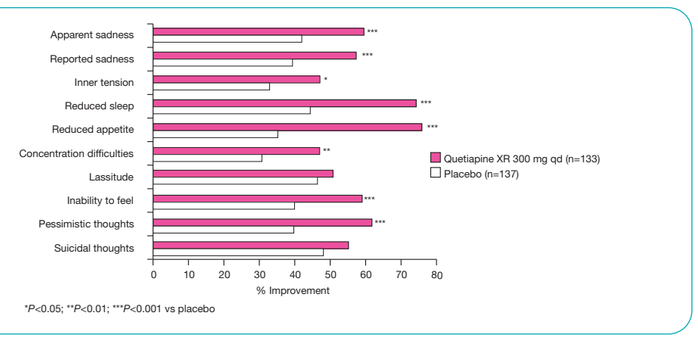
Figure 4. Mean change in MADRS total score in patients with and without a rapid cycling disease course (OC, MMRM)



Improvement in MADRS individual items

- Quetiapine XR 300 mg qd significantly improved 8 of the 10 individual MADRS item scores from baseline to Week 8 when compared with placebo, including apparent sadness, reported sadness, reduced sleep, reduced appetite, inability to feel, and pessimistic thoughts (all *P*<0.001), concentration difficulties (*P*<0.01), and inner tension (*P*<0.05) (**Figure 5**)

Figure 5. Percentage improvement in MADRS individual item scores from baseline at Week 8 (ITT, LOCF)

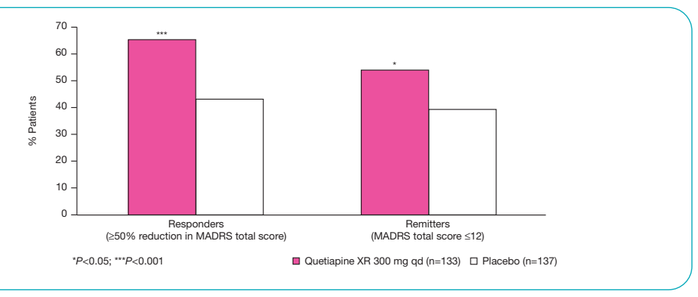


- The individual MADRS item scores for suicidal thoughts and lassitude were numerically improved with quetiapine XR 300 mg qd but these improvements were not statistically significant

MADRS response and remission

- The proportion of patients achieving response was significantly higher in the quetiapine XR 300 mg qd group compared with the placebo group from Week 2 onward until the study end (*P*<0.05 at all time points); at Week 8, 65.4% patients in the quetiapine XR 300 mg qd group versus 43.1% patients in the placebo group achieved response (*P*<0.001; **Figure 6**)
- A significantly greater proportion of quetiapine XR- than placebo-treated patients achieved remission beginning at Week 1 and continuing up to Week 8 (*P*<0.05 at all time points). At Week 8, the proportion of remitters in the quetiapine XR 300 mg qd group was 54.1% compared with 39.4% in the placebo group (*P*=0.018; **Figure 6**)

Figure 6. Proportion of patients achieving response and remission (ITT, LOCF)



CGI-BP Severity of Illness and Change (overall bipolar illness)

- Overall improvement in CGI-BP-S score for overall bipolar illness from baseline to Week 8 was significantly higher in the quetiapine XR 300 mg qd group versus the placebo group (*P*<0.001; ANCOVA, LOCF)
- The mean change in the CGI-BP-S score for overall bipolar illness from baseline to Week 8 for the quetiapine XR 300 mg qd and the placebo group was -1.82 and -1.25, respectively
- The proportion of patients with CGI-BP-C score of "much improved" or "very much improved" was significantly higher in the quetiapine XR 300 mg qd group versus the placebo group from Week 1 to the study end (*P*<0.05). At Week 8, 63.2% of the patients in the quetiapine XR 300 mg qd group versus 39.4% of the patients in the placebo group (*P*<0.001) had CGI-BP-C scores of "much improved" or "very much improved". The majority of the remaining patients had CGI-BP-C scores of "minimally improved" or "no change"

Safety

Adverse events

- The proportion of patients reporting any AEs was 88.3% in the quetiapine XR 300 mg qd group versus 68.6% in the placebo group
- The proportion of patients who withdrew from the study was slightly higher in the quetiapine 300 mg qd group compared with the placebo group (**Table 2**). The proportion of patients discontinuing due to AEs was higher in the quetiapine XR 300 mg qd group compared with the placebo group. The proportion of patients with an SAE was similar (~1.5%) in both groups, and there were no incidences of death reported in either of the groups

Table 2. Disposition of patients who discontinued the study (all randomized patients)

Study discontinuation, n (%)	Quetiapine XR 300 mg qd (n=140)	Placebo (n=140)
Patients who discontinued study	52 (37.1)	42 (30.0)
Incorrect enrollment	0 (0)	2 (1.4)
Severe noncompliance to protocol	4 (2.9)	5 (3.6)
Safety reasons	1 (0.7)	0 (0)
Adverse events	17 (12.1)	2 (1.4)
Condition under investigation worsened	3 (2.1)	4 (2.9)
Lack of therapeutic response	2 (1.4)	10 (7.1)
Lost to follow-up	12 (8.6)	8 (5.7)
Voluntary discontinuation	12 (8.6)	10 (7.1)
Other	1 (0.7)	1 (0.7)

- The most common AEs observed in the quetiapine XR 300 mg qd group were dry mouth, somnolence, and sedation (**Table 3**)

Table 3. Adverse events (those occurring in ≥5% patients in the quetiapine XR 300 mg qd group) (safety population)

Adverse events, n (%)	Quetiapine XR 300 mg qd (n=137)	Placebo (n=140)
Dry mouth	51 (37.2)	10 (7.1)
Somnolence	40 (29.2)	8 (5.7)
Sedation	32 (23.4)	10 (7.1)
Dizziness	18 (13.1)	15 (10.7)
Increased appetite	17 (12.4)	8 (5.7)
Headache	13 (9.5)	14 (10.0)
Constipation	11 (8.0)	9 (6.4)
Nausea	10 (7.3)	10 (7.1)
Weight increase	10 (7.3)	2 (1.4)
Dyspepsia	9 (6.6)	1 (0.7)
Fatigue	8 (5.8)	3 (2.1)

- The most common AEs reported with quetiapine XR 300 mg qd were similar to those previously reported for quetiapine IR in other bipolar depression studies (BipOLar DEpRession [BOLDER] I and II and acute phase of Efficacy of Monotherapy Seroquel in BipOLar DEpressioN [EMBOLDEN] I and II)[4-7]; no additional unexpected AEs were reported in this study
- The incidence of AEs potentially related to EPS (which included akathisia, dystonia, extrapyramidal disorder, hypertonia, and tremor) was relatively low in both groups: 4.4% in quetiapine XR 300 mg qd group versus 0.7% in the placebo group. Use of anticholinergic medications was low and similar in both groups (<1%)
- The proportion of patients with worsened SAS scores at Week 8 was 6.9% in the quetiapine XR 300 mg qd group versus 4.5% in the placebo group; 75.0% and 78.8%, respectively, showed no change in SAS scores
- The proportion of patients with worsened BARS scores at Week 8 was 4.3% in the quetiapine XR 300 mg qd group versus 1.5% in the placebo group, and 79.3% versus 87.1%, respectively, had no change in BARS scores

Treatment-emergent mania

- There were no incidents of AEs associated with mania/hypomania in either treatment group. The incidence of treatment-emergent mania was lower in the quetiapine XR 300 mg qd group than in the placebo group: 6 (4.4%) versus 9 (6.4%), respectively

Suicidality

- The incidence of AEs related to suicidal behavior/ideation as evaluated by a classification system similar to the Columbia Classification criteria was low and comparable across both groups: quetiapine XR 300 mg qd 1 (0.7%); placebo 2 (1.4%)

Changes in laboratory and metabolic parameters

- Mean weight change at Week 8 was greater in patients treated with quetiapine XR 300 mg qd (+1.3 kg) than in those receiving placebo (-0.2 kg). At final assessment, 8.2% of patients in the quetiapine XR 300 mg qd group and 0.8% patients in the placebo group had a ≥7% increase in weight
- For fasting glucose levels, the proportion of patients with shifts to clinically important high values (≥7mmol/L) at Week 8 was higher in the quetiapine XR 300 mg qd group (5.8%) than in the placebo group (2.1%)
- The mean change from baseline in serum glucose levels in the overall safety population was similar in both the study groups: 0.34 mmol/L in the quetiapine XR 300 mg qd group versus 0.33 mmol/L in the placebo group. Mean changes in serum glucose levels were also evaluated based on diabetic risk factors. Diabetic risk factors were defined as fasting glucose ≥100 and <126 mg/dL at randomization, history of diabetes or obesity, or BMI ≥35 kg/m^2
  - Mean change from baseline in serum glucose levels in patients with diabetic risk factors was 0.44 mmol/L in the quetiapine XR 300 mg qd group versus 0.31 mmol/L in the placebo group
  - In patients without diabetic risk factors, mean change from baseline in serum glucose levels in the quetiapine XR 300 mg qd group was 0.24 mmol/L versus 0.33 mmol/L in the placebo group
- For total cholesterol levels, the proportion of patients with shifts from values outside the clinically important range at baseline to clinically important high values (≥6.21 mmol/L) at Week 8 was higher in the quetiapine XR 300 mg qd treatment group (7.1%) than in the placebo group (2.8%).
- For triglyceride levels, 8.3% of the patients in the quetiapine XR 300 mg qd group versus 7.5% of the patients in the placebo group were reported to have shifts from values outside the clinically important range at baseline to clinically important high values (≥2.26 mmol/L) at Week 8

Conclusions

- **In this study, quetiapine XR 300 mg qd monotherapy was more effective than placebo for the treatment of acute depressive episodes in patients with bipolar I or II disorder**
- **Quetiapine XR 300 mg qd was effective in rapidly reducing the overall symptoms associated with episodes of depression in patients with bipolar disorder, as was evident by improvement in the primary outcome measure and several of the secondary outcome measures from the first week onward, which was sustained throughout the study period**
- **Quetiapine XR 300 mg qd was effective in decreasing symptoms of depression in both patients with and without a rapid cycling disease course**
- **Quetiapine XR 300 mg qd was generally well tolerated in patients with bipolar disorder (I or II) experiencing acute episodes of depression**
- **Treatment with quetiapine XR 300 mg qd monotherapy was associated with greater weight gain than placebo. Those patients at risk for diabetes, as defined by pre-treatment parameters, experienced higher mean changes in laboratory parameters of glucose regulation, while for those patients not at risk for diabetes as defined above, there was a lower mean change in serum glucose levels in the quetiapine group compared with the placebo group. Further studies are needed to understand and clarify the effects on glucose regulation in different subgroups**
- **Results of this study further confirm the benefits of quetiapine monotherapy for the treatment of acute depressive episodes in patients with bipolar disorder, an illness that when untreated is associated with an approximate 15% completed suicide risk. Treatment benefits observed with quetiapine in this study are consistent with those reported in other landmark studies of quetiapine IR including the BOLDER I and II studies and the acute phase of the EMBOLDEN I and II studies[4-7]**

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AE, adverse event; ANCOVA, analysis of covariance; BARS, Barnes Akathisia Rating Scale; BMI, body mass index; CGI-BP, Clinical Global Impression-Bipolar; CGI-BP-C, Clinical Global Impression-Bipolar-Change; CGI-BP-S, Clinical Global Impression-Bipolar-Severity of Illness; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; EPS, extrapyramidal symptoms; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; IR, immediate release; ITT, intent to treat; LOCF, last observation carried forward; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, Mixed Model Repeated Measures; OC, observed cases; SAE, serious adverse event; SAS, Simpson-Angus Scale; SD, standard deviation; XR, extended release; YMRS, Young Mania Rating Scale

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