A Double-Blind, Placebo-Controlled Study of Quetiapine and Lithium Monotherapy in Adults in the Acute Phase of Bipolar Depression (EMBOLDEN I)

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Objective: The aim of this study was to compare the efficacy and tolerability of quetiapine and lithium monotherapy with that of placebo for a major depressive episode in bipolar disorder.

Method: 802 patients with *DSM-IV*–defined bipolar disorder (499 bipolar I, 303 bipolar II) were randomly allocated to quetiapine 300 mg/d (n = 265), quetiapine 600 mg/d (n = 268), lithium 600 to 1800 mg/d (n = 136), or placebo (n = 133) for 8 weeks. Primary endpoint was the change in Montgomery-Asberg Depression Rating Scale (MADRS) total score. The study was conducted from August 2005 to May 2007.

Results: Mean MADRS total score change from baseline at week 8 was –15.4 for quetiapine 300 mg/d, –16.1 for quetiapine 600 mg/d, –13.6 for lithium, and –11.8 for placebo ($P < .001$ for both quetiapine doses, $P = .123$ for lithium, vs placebo). Quetiapine 600 mg/d was significantly more effective than lithium in improving MADRS total score at week 8 ($P = .013$). Quetiapine-treated (both doses), but not lithium-treated, patients showed significant improvements ($P < .05$) in MADRS response and remission rates, Hamilton Depression Rating Scale (HDRS), Clinical Global Impressions-Bipolar-Severity of Illness and -Change, and Hamilton Anxiety Rating Scale (HARS) scores at week 8 versus placebo. Both quetiapine doses were more effective than lithium at week 8 on the HDRS and HARS. The most common adverse events were somnolence, dry mouth, and dizziness with quetiapine (both doses) and nausea with lithium.

Conclusions: Quetiapine (300 or 600 mg/d) was more effective than placebo for the treatment of episodes of acute depression in bipolar disorder. Lithium did not significantly differ from placebo on the main measures of efficacy. Both treatments were generally well tolerated.

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See companion EMBOLDEN II article.

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The impact of mental health–related disorders on the global burden of disease is substantial. Over a quarter of the disease burden worldwide is attributed to mental disorders and other neuropsychiatric conditions compared with 22% for cardiovascular disease and 11% for cancer.[1] Bipolar disorder, and in particular the depressive phase, ranks high among the major contributors to the greater disability associated with mental disorders.[1]

Depression dominates the course of bipolar disorder and is associated with significant morbidity and mortality.[2,3] Nonetheless, the treatment of acute depressive episodes in bipolar disorder remains understudied and controversial. Most treatment guidelines for bipolar disorder advocate first-line monotherapy with conventional "mood stabilizers," especially lithium, for mild to moderate episodes of depression.[3–8] However, the empirical evidence supporting the antidepressant efficacy of lithium is currently limited.

Although historically lithium has demonstrated putative antidepressant efficacy in older studies, in more recent stringent investigations, the response to lithium of patients with bipolar depression has been more modest.[9,10] Moreover, achievement of an antidepressant effect with lithium may take several weeks,[11] which is a notable disadvantage in the acute treatment setting. Traditional antidepressants (such as monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and tricyclic antidepressants), well-established treatments for major depression, are also used alone or in combination with mood stabilizers for the treatment of bipolar depression. The use of antidepressants, however, has been the focus of controversy because of the potential risk of switching to mania or hypomania during treatment.[12–14] Alternative treatments such as lamotrigine have also been investigated. The efficacy of lamotrigine as maintenance treatment for bipolar disorder, particularly for delaying depressive episodes, is well established, but

its efficacy in the acute treatment of bipolar depression is less clear.[15]

More recently, second-generation antipsychotics have been shown to be effective in acute bipolar disorder. The olanzapine-fluoxetine combination (OFC) and quetiapine have each received registrations in the United States for acute bipolar depression. The efficacy of OFC or olanzapine monotherapy versus placebo was investigated in an 8-week study of 833 patients with acute bipolar I depression.[16] Change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS)[17] total score indicated significantly greater symptom improvements with olanzapine and OFC compared with placebo at study end point. Additionally, OFC demonstrated greater reductions in MADRS total score than olanzapine from week 4 onward. The efficacy of quetiapine monotherapy (300 mg/d and 600 mg/d) in bipolar depression was initially demonstrated in 2 large, 8-week studies (BipOLar DEpRession [BOLDER] I and II).[18,19] In these studies, quetiapine (both doses) significantly improved symptoms of depression compared with placebo at week 8, as demonstrated by a greater reduction in MADRS total score from baseline. Furthermore, a significantly higher proportion of quetiapine-treated patients met criteria for response and remission than patients in the placebo group. Notably, quetiapine was not associated with an increased risk of treatment-emergent mania or hypomania compared with placebo. Recent guideline recommendations for first- and second-line treatment of acute bipolar depression reflect these clinical trial data and registrations.[20,21]

Given the limited evidence for effective treatments for bipolar depression, emerging results from monotherapy trials such as BOLDER are promising. However, head-to-head comparisons between established and newer treatments are lacking, which hinders the identification of a gold-standard treatment for acute bipolar depression. The present study (Efficacy of Monotherapy Seroquel in BipOLar DEpressioN I [EMBOLDEN I]) is one of 2 large similarly designed studies (a total of 1,542 patients randomized) that compared the efficacy and tolerability of quetiapine monotherapy with that of placebo for the acute treatment (8 weeks) of bipolar I and II disorder (most recent episode depression) followed by a 26- to 52-week continuation treatment phase. The studies also included lithium (EMBOLDEN I) and paroxetine (EMBOLDEN II; see companion article[46]) comparator arms. Results from the acute treatment phase of EMBOLDEN I are presented here.

METHOD

This study was an 8-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, fixed-dose trial assessing the efficacy and tolerability of quetiapine and lithium monotherapy for episodes of major depression in patients with bipolar I and II disorder. The study, conducted at 110 centers throughout Europe, Canada, and Asia, conformed to the current amendment of the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. Approval for the study was obtained from either a central institutional review board or a review board at the study site. All patients provided written informed consent prior to participation in the study. The first patient was enrolled in August 2005, and the last patient completed the study in May 2007.

Once enrolled, patients underwent a washout period of at least 5 to 28 days, during which prior psychotropic medications were discontinued. Patients were subsequently randomly assigned to receive acute treatment with quetiapine (300 or 600 mg/d), lithium (600–1,800 mg/d), or placebo for 8 weeks. Eligible patients, those with both MADRS and Young Mania Rating Scale (YMRS)[22] total scores of ≤ 12 at the end of the acute treatment phase, could then enter a 26- to 52-week continuation treatment phase with quetiapine (300 or 600 mg/d) versus placebo. Continuation-phase data will be published separately.

Patient Population

Adult outpatients (aged 18–65 years) meeting *DSM-IV* criteria for bipolar I or II disorder (with or without rapid cycling; ≥ 4 episodes/year to ≤ 8 per year) and who were experiencing a recent major depressive episode (duration ≤ 1 year and onset ≥ 4 weeks) prior to entry were eligible for inclusion in the study. Patients were also required to demonstrate a Hamilton Depression Rating Scale (HDRS)[23] score ≥ 20 and an HDRS item 1 (depressed mood) score ≥ 2.

Key exclusion criteria were (1) active Axis I disorders requiring treatment within 6 months of study entry; (2) a YMRS total score > 12; (3) a history of nonresponse to an adequate treatment period (6 weeks) with ≥ 2 classes of antidepressants during the current episode; (4) known nonresponse to quetiapine or lithium, as judged by the investigator; (5) substance dependence (*DSM-IV*) or abuse; (6) a current serious suicidal or homicidal risk (as judged by the investigator); and (7) a clinically relevant medical illness.

Treatment randomization, using an interactive response system, was stratified by bipolar diagnosis (I or II) in order to achieve an approximate balance between the 2 bipolar subtypes. Within each stratum, patients entering the acute treatment phase were randomly assigned in a 2:2:1:1 ratio to receive quetiapine 300 mg/d, quetiapine 600 mg/d, lithium 600 to 1,800 mg/d, or placebo. The randomization was centralized, and randomization numbers were not sequential within a site. No member of the investigational team had access to the randomization scheme during the conduct of the study. To ensure that study participants and study investigators were blinded to treatment allocation, all medication packaging was identical, with active tablets identical in size, color, smell, and taste to the

placebo tablets. A double-dummy method was employed, and the number of tablets dispensed was identical across all treatment arms.

Study Treatments

Quetiapine or matching placebo was administered orally once a day at bedtime. Quetiapine was initiated at a dose of 50 mg/d and then increased to achieve a target dose of 300 mg/d by day 4 or 600 mg/d by day 8. Lithium or matching placebo was administered twice daily (morning and bedtime). Lithium was initiated at 600 mg/d and subsequently increased to 900 mg/d from day 4 until day 8. Lithium was dosed thereafter in a blinded manner at 600 to 1,800 mg/d to maintain a serum lithium concentration between 0.6 and 1.2 mEq/L.

Prior and Concomitant Medication

During the study, continuation of nonpsychotropic medications taken prior to study entry was permitted. Lorazepam (1–3 mg/d for severe anxiety) and hypnotics (zolpidem tartrate up to 10 mg/d, zaleplon up to 20 mg/d, zopiclone up to 7.5 mg/d, or chloral hydrate up to 1 g/d at bedtime for insomnia) were allowed during the first 3 weeks of treatment at the investigator's discretion. Concomitant treatment with all other psychotropic drugs was prohibited during the study.

Efficacy Assessments

The primary efficacy outcome measure was the change from baseline to week 8 in MADRS total score. Secondary efficacy outcome measures included response (≥ 50% reduction in MADRS total score) and remission (MADRS total score ≤ 12) rates and Clinical Global Impressions-Bipolar-Change[24] response at week 8. Additional efficacy measures were change from baseline to week 8 in MADRS individual items, MADRS item 10 (suicidal thoughts), HDRS total score, HDRS item 1 (depressed mood), Clinical Global Impressions-Bipolar-Severity of Illness (CGI-BP-S),[24] and the Hamilton Anxiety Rating Scale (HARS).[25] Patient-reported changes from baseline in the Sheehan Disability Scale (SDS)[26] and the Medical Outcomes Study Cognitive Scale (MOS-Cog)[27] were used to evaluate treatment effects on social, occupational, and cognitive functioning. Assessments of efficacy were performed at baseline, at weeks 1 and 2, and then every 2 weeks until week 8, except for SDS and MOS-Cog, which were assessed at baseline and at weeks 4 and 8 only.

Safety and Tolerability Assessments

Safety and tolerability assessments included adverse events (AEs; incidence and severity), withdrawals due to AEs, and extrapyramidal symptoms (EPS; measured using the Simpson Angus Scale [SAS][28] and the Barnes Akathisia Rating Scale [BARS][29]), as well as laboratory tests, weight and body mass index, electrocardiogram (ECG), physical examination, and vital signs. In addition, the proportion of patients with treatment-emergent mania or hypomania (defined as a YMRS total score ≥ 16 on 2 consecutive assessments or at final assessment, or an AE report of treatment-emergent mania or hypomania) or treatment-emergent suicidal ideation (incidence of patients with HDRS item 3 [suicide] score ≥ 3 or an AE of suicidality, suicidal ideation, suicide attempts, or suicide completion) was assessed.

Statistical Analysis

Efficacy analyses were conducted in the intent-to-treat (ITT) population (patients who received at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment) using last-observation-carried-forward methodology to deal with missing data from patient dropout in the efficacy analyses. Secondary analyses were conducted in the per protocol (PP) population (patients who completed study treatment without major protocol violations or deviations affecting efficacy) to test the robustness of the ITT findings. Patients with a median serum lithium concentration below 0.6 or above 1.2 mEq/L were excluded from the PP population. It was estimated that sample sizes would provide 87% power to detect 4 points difference between each quetiapine dose and placebo in MADRS total score change from baseline to week 8 with a pooled standard deviation of 10 using a 2-sided test at an α level of .025 (Bonferroni corrected). No power calculations were made for a non-inferiority comparison between quetiapine and lithium treatment groups.

The primary efficacy outcome measure of change from baseline in MADRS total score tested the efficacy of quetiapine 300 or 600 mg/d versus placebo using analysis of covariance (ANCOVA) with baseline MADRS total score as the covariate, treatment and diagnosis strata as fixed effects, and country as a random effect in the model. A similar ANCOVA model was also used for other continuous efficacy measures. MADRS response and remission were analyzed using Cochran-Mantel-Haenszel test stratified by bipolar diagnosis. The number needed to treat (NNT) in order to achieve response and remission outcomes was also calculated for each active treatment group versus placebo. Statistical analysis of safety end points was not planned in the study protocol. Analyses of safety variables, including AEs, are presented descriptively. The safety population comprised patients who received at least 1 dose of the study medication.

RESULTS

Patients

A total of 802 patients with bipolar I or II disorder experiencing an episode of depression were randomly allocated to treatment with quetiapine 300 mg/d (n = 265), quetiapine 600 mg/d (n = 268), lithium 600 to 1,800 mg/d (n = 136), or placebo (n = 133) for 8 weeks (Figure 1). Of these, 794 patients were included in the safety population, and 783

Figure 1. Patient Disposition in the Acute Treatment Phase

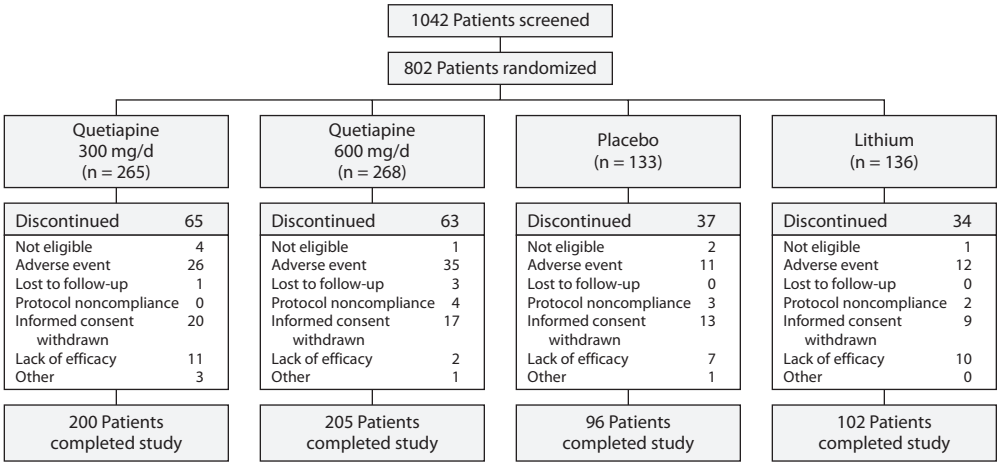

Table 1. Baseline Patient Demographics and Disease Characteristics (ITT; acute treatment phase)

Characteristic	Quetiapine 300 mg/d (n = 255)	Quetiapine 600 mg/d (n = 263)	Placebo (n = 129)	Lithium (n = 136)
Sex, %				
Men	42.7	36.5	45.7	40.4
Women	57.3	63.5	54.3	59.6
Age, mean, y	42.3	42.8	41.5	41.4
Weight, mean, kg	75.8	74.4	76.0	77.0
Bipolar disorder type, %				
Bipolar I	62.7	61.6	60.5	64.0
Bipolar II	37.3	38.4	39.5	36.0
Rapid-cycling course (≥ 4 mood episodes in past year), %	6.3	6.1	3.9	5.9
Non-rapid-cycling course, %	93.7	93.9	96.1	94.1
MADRS total score, mean	28.1	28.3	28.5	28.3
HDRS total score, mean	24.2	24.3	24.4	24.1
YMRS total score, mean	3.1	3.3	3.3	3.4
HARS total score, mean	18.3	18.2	18.3	18.0
CGI-BP-S score, mean	4.4	4.3	4.3	4.4

Abbreviations: CGI-BP-S = Clinical Global Impressions-Bipolar-Severity of Illness, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, ITT = intent-to-treat, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

and 704 patients were included in the efficacy ITT and PP populations, respectively. Baseline characteristics did not markedly differ between treatment groups (Table 1). In the overall population, the mean age was 42.2 years, and the majority of patients were women (59.3%). The mean median daily dose and serum concentration of lithium in the ITT population were 981 mg and 0.61 mEq/L, respectively. In total, 83 (64.4%) patients in the lithium group achieved median serum concentrations of lithium that were in the target serum concentration range of 0.6 to 1.2 mEq/L, while 45 (34.9%) patients had median serum concentrations of lithium below 0.6 mEq/L.

Similar proportions of patients completed the acute treatment phase of the study (75.5%, 76.5%, and 75.0% in the quetiapine 300 mg/d, quetiapine 600 mg/d, and lithium groups, respectively, vs 72.2% with placebo). Patient disposition is shown in Figure 1.

Efficacy

MADRS. Starting at week 1 (first assessment) and continuing through week 8, both doses of quetiapine (300 and 600 mg/d) were significantly better than placebo at improving MADRS total scores in the ITT population ($P < .05$; Figure 2A, Table 2). Lithium-treated patients demonstrated numerically greater but not statistically significant improvement in MADRS total score compared with placebo throughout 8 weeks of treatment (Figure 2A; at week 8, –13.6; $P = .123$). Further post hoc analysis of the lithium treatment group, in which patients with median serum lithium concentrations ≥ 0.8 mEq/L were analyzed separately (n = 34; ITT population), revealed no difference from placebo in terms of the improvement in MADRS total score from baseline (difference of –2.76 points at week 8; $P = .128$).

Quetiapine 600 mg/d (but not 300 mg/d) significantly improved MADRS total score compared with lithium from day 8 through week 8 (difference of –2.49 points at week 8, $P = .013$).

Similar results were observed in the PP population. In the PP population, throughout 8 weeks of treatment, the magnitude of improvements in MADRS total score for quetiapine 300 mg/d (–15.7; $P < .001$) and 600 mg/d (–16.5; $P < .001$) was greater compared with placebo (–12.1). Improvements in MADRS total scores for lithium-treated patients (n = 87) in the PP population (mean median lithium concentration 0.7 mEq/L) did not differ significantly from placebo-treated patients (n = 126) from day 8 through study end (at week 8, –13.3; $P = .349$). Significant improvements in MADRS total scores were observed for quetiapine 300 mg/d (n = 241) and

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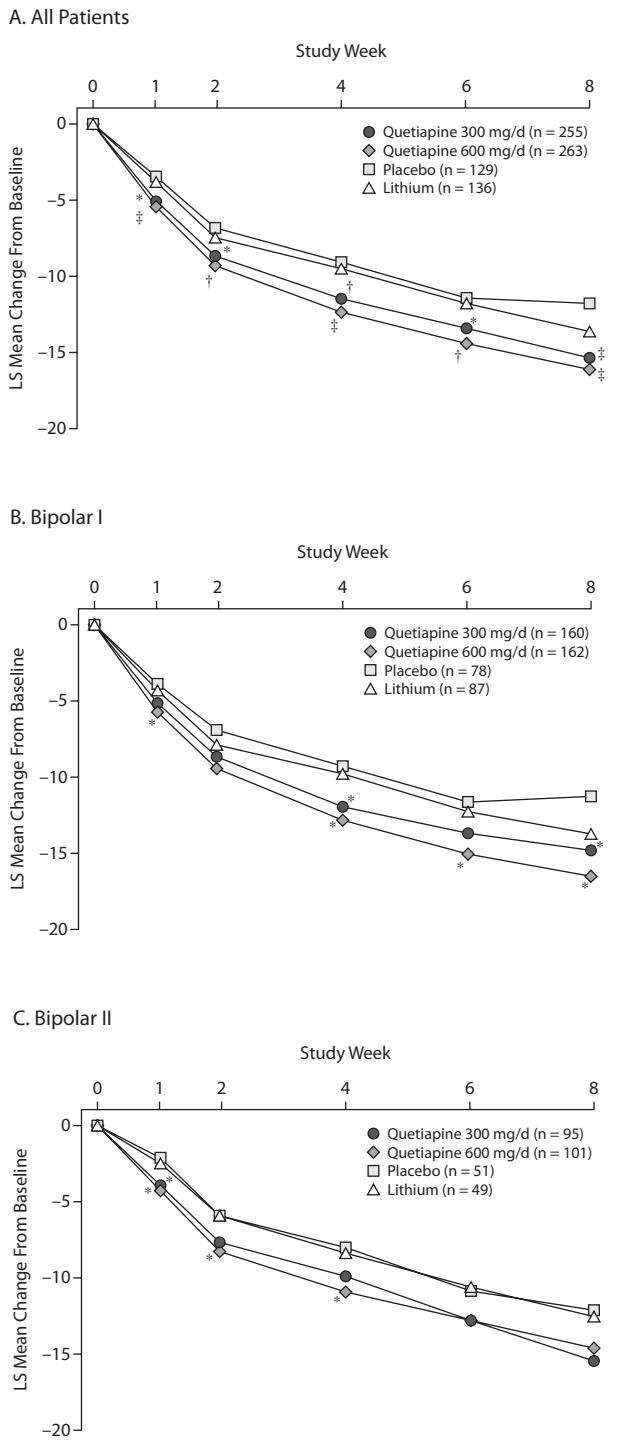
Figure 2. Mean Change From Baseline in MADRS Total Score in Patients With Bipolar I or II Disorder (ITT; LOCF; acute treatment phase)



*$P < .05$, †$P < .01$, ‡$P < .001$ vs placebo.
Abbreviations: ITT = intent-to-treat, LOCF = last observation carried forward, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale.

600 mg/d (n = 250) when compared with lithium at week 8 (300 mg/d: difference of –2.35 points, 95% CI, –4.66 to –0.04; 600 mg/d: difference of –3.16 points, 95% CI, –5.46 to –0.86).

In patients with bipolar I disorder, quetiapine treatment (both doses) significantly improved MADRS total scores compared with placebo (difference of –3.61 points at week 8 for quetiapine 300 mg/d [n = 160], $P = .006$; difference of –5.28 points for quetiapine 600 mg/d [n = 162], $P < .001$) (Figure 2B). In patients with bipolar II disorder, patients treated with quetiapine (both doses) showed numerically greater improvements in MADRS total scores at week 8 (300 mg/d [n = 95]: difference of –3.19 points, $P = .051$; 600 mg/d [n = 101]: difference of –2.43 points, $P = .131$) (Figure 2C). Patients without a rapid-cycling disease course showed significantly greater improvement over placebo (n = 128) at week 8 in MADRS score when treated with quetiapine 300 mg/d (difference, –3.80; $P < .001$ [n = 239]) or quetiapine 600 mg/d (difference, –4.56; $P < .001$ [n = 247]), but not with lithium (difference, –2.15; $P = .066$ [n = 124]). For the relatively few patients with a rapid-cycling disease course (n = 45), the difference in change from baseline to week 8 in MADRS total score compared with placebo was 2.82 ($P = .607$) for quetiapine 300 mg/d, 0.76 ($P = .889$) for quetiapine 600 mg/d, and 6.92 ($P = .275$) for lithium.

At end point (week 8), significantly more patients treated with quetiapine met response criteria than those who received placebo: 68.6% for quetiapine 300 mg/d ($P < .05$) and 69.6% for quetiapine 600 mg/d ($P < .01$) versus 55.8% for placebo, with NNTs of 8 and 7 for quetiapine 300 mg/d and quetiapine 600 mg/d, respectively. Patients treated with lithium demonstrated a numerically greater response (62.5%) than those receiving placebo (NNT = 15), but the difference was not statistically significant ($P = .279$). At end point (week 8), significantly more patients met remission criteria in the quetiapine 300 mg/d (69.8%) and quetiapine 600 mg/d (70.3%) groups than in the placebo group (55.0%; $P < .01$ both doses), while 62.5% of patients in the lithium group met remission criteria ($P = .228$ vs placebo). The corresponding NNTs were 7, 7, and 13 for quetiapine 300 mg/d, quetiapine 600 mg/d, and lithium, respectively. Of those patients meeting remission criteria, the following proportions had MADRS total scores < 24 at baseline: 28.2% of the placebo group; 27.5% and 23.2% of the quetiapine 300 mg/d and 600 mg/d groups, respectively; and 24.7% of the lithium group.

By week 8, there were significant improvements compared with placebo in 7 of 10 individual MADRS items with quetiapine 300 mg/d ($P < .05$) and 9 of 10 items with quetiapine 600 mg/d ($P < .05$); only 2 items (inner tension and reduced sleep) were significantly improved following treatment with lithium ($P < .05$) (Figure 3). At week 8, quetiapine 600 mg/d was significantly better than lithium in improving the following individual MADRS item scores: apparent sadness (difference –0.42 points, $P = .003$), reported sadness

Table 2. Mean Change From Baseline in Primary and Secondary Outcome Measures (ITT population; LOCF; acute treatment phase)

Measure and Treatment	Baseline Score Mean	Baseline Score SE	Change in Score at End of Acute Treatment Phase, LS Mean (SE)	Analysis (comparison with placebo) ANCOVA, LS Mean (SE)	Analysis (comparison with placebo) *P* Value
Montgomery-Asberg Depression Rating Scale					
Quetiapine 300 mg/d, n = 255	28.1	0.39	−15.36 (0.93)	−3.55 (1.02)	< .001
Quetiapine 600 mg/d, n = 263	28.3	0.40	−16.10 (0.92)	−4.29 (1.02)	< .001
Placebo, n = 129	28.5	0.54	−11.81 (1.10)		
Lithium, n = 136	28.3	0.48	−13.60 (1.08)	−1.79 (1.16)	.123
Hamilton Depression Rating Scale					
Quetiapine 300 mg/d, n = 255	24.2	0.22	−13.98 (0.78)	−3.26 (0.83)	< .001
Quetiapine 600 mg/d, n = 263	24.3	0.21	−14.17 (0.77)	−3.45 (0.82)	< .001
Placebo, n = 129	24.4	0.28	−10.72 (0.91)		
Lithium, n = 136	24.1	0.28	−12.36 (0.90)	−1.64 (0.94)	.082
Hamilton Depression Rating Scale item 1 (depressed mood)					
Quetiapine 300 mg/d, n = 255	2.9	0.03	−1.52 (0.10)	−0.26 (0.11)	.023
Quetiapine 600 mg/d, n = 263	3.0	0.04	−1.62 (0.10)	−0.36 (0.11)	.001
Placebo, n = 129	3.0	0.05	−1.26 (0.12)		
Lithium, n = 136	2.9	0.05	−1.36 (0.12)	−0.10 (0.13)	.438
Clinical Global Impressions-Bipolar-Severity of Illness					
Quetiapine 300 mg/d, n = 255	4.4	0.05	−1.51 (0.13)	−0.37 (0.14)	.008
Quetiapine 600 mg/d, n = 263	4.3	0.04	−1.57 (0.13)	−0.43 (0.14)	.002
Placebo, n = 129	4.3	0.07	−1.14 (0.15)		
Lithium, n = 135	4.4	0.07	−1.40 (0.15)	−0.26 (0.16)	.098
Hamilton Anxiety Rating Scale					
Quetiapine 300 mg/d, n = 255	18.3	0.40	−9.14 (0.63)	−2.60 (0.71)	< .001
Quetiapine 600 mg/d, n = 263	18.2	0.37	−9.29 (0.63)	−2.75 (0.70)	< .001
Placebo, n = 129	18.3	0.51	−6.55 (0.75)		
Lithium, n = 136	18.0	0.47	−7.72 (0.74)	−1.17 (0.80)	.144
Sheehan Disability Scale					
Quetiapine 300 mg/d, n = 244	19.3	0.33	−6.90 (0.78)	−1.57 (0.77)	.041
Quetiapine 600 mg/d, n = 248	18.7	0.35	−7.54 (0.78)	−2.21 (0.76)	.004
Placebo, n = 124	18.3	0.51	−5.33 (0.89)		
Lithium, n = 131	19.4	0.45	−7.00 (0.88)	−1.67 (0.87)	.056
Medical Outcomes Study Cognitive scale					
Quetiapine 300 mg/d, n = 244	18.8	0.31	5.67 (0.55)	1.03 (0.66)	.120
Quetiapine 600 mg/d, n = 248	18.7	0.33	6.34 (0.55)	1.70 (0.66)	.010
Placebo, n = 124	19.3	0.46	4.64 (0.66)		
Lithium, n = 131	19.5	0.49	5.98 (0.65)	1.34 (0.75)	.075

Abbreviations: ANCOVA = analysis of covariance, ITT = intent-to-treat, LOCF = last observation carried forward, LS = least squares.

(difference, –0.37; *P* = .008), reduced sleep (difference, –0.42; *P* = .004), and inability to feel (difference, –0.34; *P* = .011); quetiapine 300 mg/d was significantly better than lithium in improving MADRS item 4 (reduced sleep) score (difference, –0.48; *P* = .001). Improvement in suicidal thoughts was significantly greater with quetiapine 600 mg/d (*P* < .05) than placebo from week 4 to week 8; quetiapine 300 mg/d and lithium showed numerical but not statistical improvement over placebo during the 8 weeks of treatment.

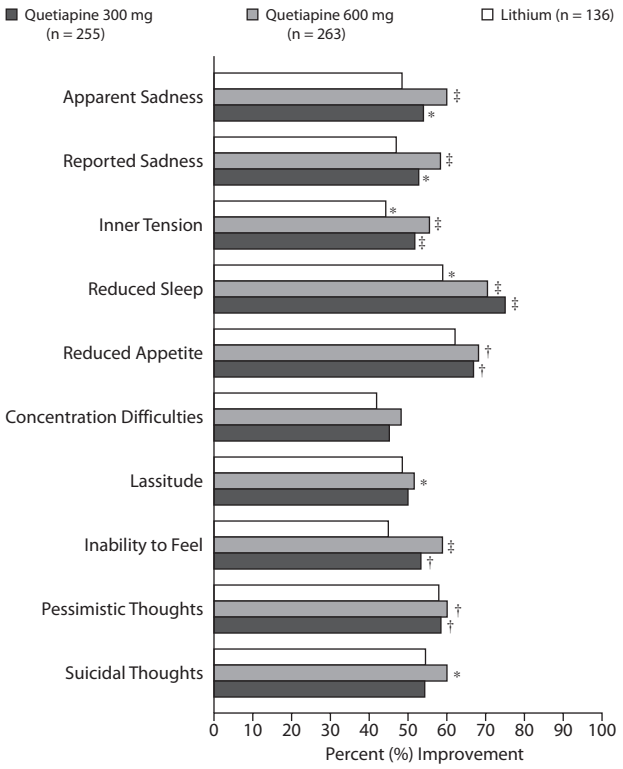
HDRS. Patients receiving quetiapine (both doses) showed significantly greater improvements in HDRS total score compared with placebo at every assessment (from week 1–week 8; *P* < .001 at end point) (Table 2). Lithium-treated patients did not show significant improvements versus placebo at any time during the acute treatment phase. At week 8, both doses of quetiapine were significantly better than lithium in improving the HDRS total score (difference, –1.62; *P* = .047 for quetiapine 300 mg/d; difference, –1.81; *P* = .026 for quetiapine 600 mg/d). Patients receiving quetiapine 600 mg/d also had significantly greater improvements in the HDRS item 1 (depressed mood) score compared with placebo (*P* < .05) and lithium at weeks 4, 6, and 8 (difference, –0.26; *P* = .018 at end point). Quetiapine 300 mg/d but not lithium was significantly better than placebo at improving the depressed mood item at week 8 (*P* < .05).

CGI-BP. At week 8, compared with patients receiving placebo, quetiapine-treated patients demonstrated significantly greater improvement in mean CGI-BP-S total score, whereas lithium-treated patients showed nonsignificant improvement (Table 2). At week 8, significantly more patients treated with quetiapine 300 or 600 mg/d were "much improved" or "very much improved" compared with placebo (64.7% and 61.6%, respectively, vs 48.1%; *P* < .05 both doses); lithium treatment resulted in numerical but not significant improvement (51.1%; *P* = .631) compared with placebo.

HARS. Both doses of quetiapine were associated with significant (*P* < .05) improvement in HARS scores compared with placebo from week 1 through week 8, while lithium was associated with only numerical improvements in this measure (Table 2).

Functional improvement: SDS and MOS-Cog. At week 8, quetiapine 600 mg/d demonstrated a significant

Figure 3. Mean Difference From Placebo in Change From Baseline to Week 8 in MADRS Individual Item Scores in Patients With Bipolar I or II Disorder (ITT; LOCF; acute treatment phase)



*$P < .05$, †$P < .01$, ‡$P < .001$ vs placebo. Values based on change from baseline LOCF analyses.
Abbreviations: ITT = intent-to-treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

improvement over placebo in the SDS total score ($P < .01$) and the MOS-Cog total score ($P = .01$) (Table 2). Quetiapine 300 mg/d demonstrated a significant improvement in SDS total score ($P < .05$), but only a numerical improvement in MOS-Cog total score at week 8. Lithium treatment was associated with numerical but statistically insignificant improvements in SDS and MOS-Cog total scores than placebo.

Safety and Tolerability

Adverse events. The proportion of patients discontinuing due to AEs was 10.4% and 13.9% in the quetiapine 300 and 600 mg/d groups, 8.4% in the placebo group, and 8.8% in the lithium group. The incidence of serious AEs was low and similarly distributed across the treatment groups (3.8% and 2.6% for quetiapine 300 and 600 mg/d, 2.3% for placebo, and 2.2% for lithium). The majority of AEs experienced by patients were mild to moderate in severity, with the most common AEs (occurring in > 10% of patients) reported as somnolence, dry mouth, and dizziness with quetiapine (both doses) and nausea with lithium (Table 3).

The incidence of treatment-emergent mania was low in all treatment groups, but higher in the quetiapine and lithium groups compared with placebo: 4.2% for quetiapine 300 mg/d, 2.2% for quetiapine 600 mg/d, and 2.2% for lithium, versus 0.8% for placebo. A small proportion of patients in each treatment group demonstrated treatment-emergent suicidal ideation (incidence of patients with HDRS item 3 [suicide] score ≥ 3 or an AE of suicidality, suicidal ideation, suicide attempt, or suicide completion), which was highest in the placebo group (2.3%) compared with the quetiapine 300 and 600 mg/d (1.9% and 1.1%, respectively) and lithium (0.7%) groups. Adverse events potentially related to EPS (including the MedDRA terms *akathisia, hypokinesia, restlessness, tremor, dyskinesia, extrapyramidal disorder, psychomotor hyperactivity, hyperkinesia, hypertonia, muscle rigidity,* and *nuchal rigidity*) were reported by 5.0%, 7.5%, 3.8%, and 8.1% of patients treated with quetiapine 300 mg/d, quetiapine 600 mg/d, placebo, and lithium, respectively.

The mean change in SAS total score from baseline to week 8 was similar between treatment groups (–0.1 for quetiapine 300 mg/d, 0.0 for quetiapine 600 mg/d, –0.2 for placebo, and –0.1 for lithium). There were minimal mean changes in BARS scores from baseline at week 8 in all treatment groups (0 for both quetiapine 300 and 600 mg/d, –0.1 for placebo, and 0 for lithium).

Laboratory results and vital signs. There were no clinically relevant differences between treatments in ECG measurements or vital signs. Mean changes from baseline in weight and clinical laboratory measures (glucose, lipid, and prolactin parameters) and the proportion of patients demonstrating clinically relevant changes in lipid and glucose variables were generally similar across the treatment groups (Table 4), except that the treatment groups differed in terms of effects on triglyceride levels. Triglycerides increased with quetiapine 300 and 600 mg/d, but decreased with placebo and with lithium. In addition, all treatments were associated with a decrease in prolactin levels at week 8 (Table 4). However, a higher proportion of patients treated with quetiapine 300 mg/d (10.2%) demonstrated clinically relevant increases in prolactin levels (> 20 μg/L in men or > 30 μg/L in women) than patients treated with quetiapine 600 mg/d (3.3%), placebo (4.0%), or lithium (2.8%).

DISCUSSION

This study (EMBOLDEN I) and the similarly designed EMBOLDEN II study represent 2 of the largest placebo-controlled studies to date of acute treatment in patients with bipolar I and II disorder. EMBOLDEN I replicates the antidepressant efficacy of quetiapine 300 and 600 mg/d, as initially demonstrated in the BOLDER studies.[18,19] Quetiapine treatment was associated with significant improvements in primary and secondary measures of efficacy compared with placebo. Improvements in symptoms reached significance from week 1 of treatment and were maintained up to

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Table 3. Adverse Events (≥5% in any group; safety population; acute treatment phase)[a]

	Quetiapine 300 mg/d (n = 260)			Quetiapine 600 mg/d (n = 267)			Lithium (n = 136)			Placebo (n = 131)	
Adverse Event	n	%	*P* Value (vs Placebo)	n	%	*P* Value (vs Placebo)	n	%	*P* Value (vs Placebo)	n	%
Somnolence	47	18.1	< .001	47	17.6	< .001	12	8.8	.132	5	3.8
Dry mouth	37	14.2	< .001	40	15.0	< .001	10	7.4	.035	2	1.5
Dizziness	25	9.6	.174	30	11.2	.066	6	4.4	.782	7	5.3
Headache	19	7.3	.045	23	8.6	.118	13	9.6	.341	18	13.7
Sedation	16	6.2	.042	14	5.2	.103	1	0.7	.617	2	1.5
Constipation	12	4.6	.403	21	7.9	.026	4	2.9	1.000	3	2.3
Nausea	10	3.8	.143	15	5.6	.510	23	16.9	.025	10	7.6
Diarrhea	6	2.3	.518	7	2.6	.540	9	6.6	.412	5	3.8
Insomnia	6	2.3	.138	3	1.1	.017	12	8.8	.343	7	5.3
Tremor	2	0.8	1.000	9	3.4	.176	8	5.9	.036	1	0.8

[a]Patients with multiple events in the same category are counted only once in that category.

week 8. Quetiapine monotherapy (600 mg/d) also demonstrated significant efficacy on the majority of the individual MADRS items including the core symptoms of depression (apparent sadness, reported sadness, lassitude, and suicidal thoughts). It is worth noting that the response and remission rates associated with quetiapine in this study were reported in the context of placebo response and remission rates of 55.8% and 55.0%, respectively. Although high, these findings are largely consistent with those from previous studies in bipolar depression, in which, for example, placebo response rates of 29%–50% have been reported for lamotrigine.[15] Clinical studies in major depression also report wide variability, with placebo response rates of up to 70%.[30,31] The statistical differentiation of quetiapine from placebo, in spite of these rates of placebo response, demonstrates the robust antidepressant efficacy of quetiapine.

The breadth of the therapeutic profile of quetiapine, previously shown in the BOLDER studies,[18,19] was also evident in this study. Symptomatic improvements were observed with quetiapine treatment in the subpopulations of patients with bipolar I and II disorder. Similar to the results of the BOLDER I study,[18] butnot BOLDER II,[19] improvements in MADRS total score for the smaller group of quetiapine-treated patients with bipolar II disorder did not reach statistical significance. In patients with and without rapid cycling, improvements in symptoms (change in MADRS total score) following quetiapine treatment were statistically significant only in the latter subgroup. In the BOLDER studies, MADRS total score reductions with quetiapine achieved significance versus placebo in both rapid- and non-rapid-cycling subgroups ($P \leq .01$),[18,19] possibly due to the larger sample population of rapid-cycling patients available for analysis when compared with the current study (143 in BOLDER II vs 45 in this study).

In this study, lithium treatment was associated with numerically greater, but not statistically significant, improvements in most efficacy measures compared with placebo. It should be noted, however, that the mean of the median serum lithium concentrations was at the lower end of the targeted range. A number of factors may have accounted for this finding; for example, some patients may have withdrawn from the study before the first sampling time point, or may not have had an opportunity for dose adjustment. It should also be noted that the lithium level quoted is the median concentration, and as a result, some patients may in fact have had concentrations above the lower limit of the targeted range. The lack of significance versus placebo in terms of the primary efficacy measure observed in the lithium-treated ITT population was echoed by the results from the PP population, which only included patients with a median serum lithium concentration within the targeted range. A separate analysis of patients whose median serum lithium concentrations were ≥ 0.8 mEq/L[10] yielded similar results to that with the whole lithium group and did not reveal significant improvements in MADRS total score versus placebo, although the low patient numbers probably preclude obtaining any statistically significant difference between groups. In addition, only 2 of the 10 MADRS items (inner tension and reduced sleep) significantly improved following lithium treatment compared with significant improvements in the majority of these items with quetiapine treatment.

Importantly, for some efficacy measures (MADRS and HDRS), quetiapine 600 mg/d demonstrated significantly greater improvements over lithium while quetiapine 300 mg/d showed numerical improvements over lithium. These findings are consistent with the suggestion that lithium has limited efficacy in managing symptoms of depression.[11]

Persistent depressive symptoms may have detrimental effects on functioning and quality of life in patients with bipolar disorder.[32] In addition to improvements in symptoms of depression and anxiety, both quetiapine doses showed greater improvements than placebo in social and occupational functioning according to the SDS, while quetiapine 600 mg/d showed significantly greater improvement than placebo in cognitive function, as assessed by the patient on the MOS-Cog scale.

Patients with bipolar depression are at high risk of suicide,[3,33] and, interestingly, lithium may have antisuicidal properties.[34,35] No suicides occurred in the acute treatment phase of this study, and the incidence of treatment-emergent suicidality was low across all treatment groups. Furthermore, quetiapine and lithium were associated with improvements

Table 4. Weight and Clinical Laboratory Measures (safety population; acute treatment phase)

Parameter and Treatment	Baseline Mean	Baseline SE	Change From Baseline Mean	Change From Baseline SE	*P* Value (vs placebo)	n[b]	Proportion of Patients With Clinically Relevant Changes,[a] n (%)
Weight, kg							
Quetiapine 300 mg/d	75.9	0.95	0.6	0.17	<.001	240	11 (4.6)
Quetiapine 600 mg/d	75.2	1.05	0.8	0.17	<.001	240	20 (8.3)
Placebo	75.3	1.28	−0.7	0.23	…	123	4 (3.3)
Lithium	77.5	1.54	0.2	0.19	.006	127	3 (2.4)
BMI, kg/m^2							
Quetiapine 300 mg/d	26.5	0.28	0.2	0.06	<.001	…	…
Quetiapine 600 mg/d	26.5	0.33	0.3	0.06	<.001	…	…
Placebo	26.4	0.44	−0.2	0.08	…	…	…
Lithium	27.2	0.49	0.1	0.07	.005	…	…
HbA_{1c}, %							
Quetiapine 300 mg/d	5.52	0.04	0.02	0.02	.068	224	1 (0.4)
Quetiapine 600 mg/d	5.49	0.03	0.02	0.02	.066	237	1 (0.4)
Placebo	5.46	0.04	−0.04	0.03	…	116	0 (0.0)
Lithium	5.48	0.05	−0.12	0.03	.045	115	0 (0.0)
Glucose, mg/dL							
Quetiapine 300 mg/d	95.51	0.94	2.19	1.20	.558	193	5 (2.6)
Quetiapine 600 mg/d	98.69	1.37	0.42	1.16	.684	186	8 (4.3)
Placebo	95.29	1.43	1.23	1.78	…	94	4 (4.3)
Lithium	97.54	1.54	2.40	1.70	.289	92	5 (5.4)
Insulin, pmol/L							
Quetiapine 300 mg/d	86.43	8.01	26.14	11.65	.312	…	…
Quetiapine 600 mg/d	88.69	6.94	21.51	7.75	.452	…	…
Placebo	89.27	9.34	10.52	10.51	…	…	…
Lithium	94.25	9.59	−3.58	11.99	.478	…	…
Triglycerides, mg/dL							
Quetiapine 300 mg/d	148.47	5.77	3.46	5.81	.335	181	18 (9.9)
Quetiapine 600 mg/d	151.37	6.76	9.46	5.41	.086	183	27 (14.8)
Placebo	164.35	13.57	−11.33	10.48	…	88	8 (9.1)
Lithium	147.30	9.04	−2.17	6.95	.791	92	9 (9.8)
Total cholesterol, mg/dL							
Quetiapine 300 mg/d	208.23	3.11	−5.56	2.29	.275	172	14 (8.1)
Quetiapine 600 mg/d	207.81	3.13	−2.24	2.18	.047	179	16 (8.9)
Placebo	205.64	4.26	−8.79	2.94	…	89	9 (10.1)
Lithium	206.69	4.93	−5.31	3.31	.365	86	4 (4.7)
HDL cholesterol, mg/dL							
Quetiapine 300 mg/d	55.21	0.95	−1.10	0.74	.547	189	15 (7.9)
Quetiapine 600 mg/d	57.11	1.04	−1.45	0.64	.592	209	18 (8.6)
Placebo	57.04	1.62	−0.81	0.92	…	98	9 (9.2)
Lithium	57.30	1.51	−0.55	1.10	.813	103	3 (2.9)
LDL cholesterol, mg/dL							
Quetiapine 300 mg/d	123.02	2.79	−4.56	2.00	.332	188	16 (8.5)
Quetiapine 600 mg/d	119.88	2.62	−2.61	1.99	.199	195	12 (6.2)
Placebo	116.16	3.45	−5.44	2.74	…	100	3 (3.0)
Lithium	119.88	3.94	−4.99	2.87	.647	95	5 (5.3)
Prolactin, µg/L							
Quetiapine 300 mg/d	19.22	1.72	−4.12	2.38	.567	M = 80, F = 107	M = 6 (7.5), F = 13 (12.1)
Quetiapine 600 mg/d	16.62	1.92	−3.87	1.95	.905	M = 80, F = 129	M = 4 (5.0), F = 3 (2.3)
Placebo	21.95	3.37	−7.70	2.66	…	M = 47, F = 53	M = 2 (4.3), F = 2 (3.8)
Lithium	15.40	2.17	−0.82	2.56	.534	M = 46, F = 61	M = 1 (2.2), F = 2 (3.3)

[a]At end of treatment. Clinically relevant changes defined as weight ≥ 7% increase from baseline; HbA_{1c} > 7.5%; glucose (fasting) ≥ 126 mg/dL; triglycerides ≥ 200 mg/dL; total cholesterol ≥ 240 mg/dL; HDL cholesterol ≤ 40 mg/dL; LDL cholesterol ≥ 160 mg/dL; prolactin > 20 µg/L (men) or > 30 µg/L (women).
[b]Number of patients with value below the threshold for potential clinical significance at baseline.
Abbreviations: F = female, HbA_{1c} = glycosylated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, M = male.

in suicidal thoughts as measured by item 10 on the MADRS scale, which reached significance for quetiapine 600 mg/d versus placebo. This suggests that quetiapine is unlikely to increase the risk of suicidality in acute bipolar depression in adults. However, patients at increased suicidal risk were excluded, and, as a result, this study is unable to provide conclusive evidence of treatment benefits in patients who were currently suicidal and it remains to be determined whether quetiapine will eventually be shown to have anti-suicidal properties similar to those suggested for lithium.

Treatment-emergent mania remains another clinical concern during treatment of acute bipolar depression.[12,13] In this study, the rate of treatment-emergent mania was low across all treatment groups, although rates were higher in the quetiapine 300 and 600 mg/d (4.2% and 2.2%, respectively) and lithium (2.2%) groups compared with placebo

(0.8%). In BOLDER I and II, treatment-emergent mania rates with quetiapine were similar or lower when compared with placebo, which reached significance for quetiapine 300 mg/d in BOLDER II (1.8% vs 6.6% for placebo, $P = .027$).[18,19] However, it is notable that the incidence of treatment-emergent mania in the placebo group in this study is lower than that previously reported.[18,19] Indeed, the rates of treatment-emergent mania for placebo groups in the BOLDER studies (BOLDER I, 3.9%; BOLDER II, 6.6%) were similar or higher than the rates observed for quetiapine-treated patients in this study.[18,19]

Quetiapine treatment was generally well tolerated during acute treatment. Discontinuations due to AEs were similar across the placebo, lithium, and quetiapine 300 mg/d treatment groups (8.3%–9.8%) and slightly higher in the quetiapine 600 mg/d group (13.1%). Although quetiapine monotherapy was associated with small mean increases in weight during the study and more quetiapine- than placebo-treated patients experienced a ≥ 7% increase in body weight, none of the patients discontinued the study as a result of weight gain, an important finding given the negative impact of weight gain on treatment compliance among patients with bipolar disorder.[36] Although mean changes in prolactin levels associated with either dose of quetiapine were lower than those associated with placebo, a higher proportion of patients in the quetiapine 300 mg/d group, but not in the 600 mg group, had clinically relevant increases in prolactin levels, which differs from previous studies that did not report any clinically significant differences in prolactin parameters with either dose of quetiapine and placebo.[18,19]

Adverse events experienced by patients in all treatment groups were mainly mild to moderate in intensity. Adverse events potentially related to EPS up to week 8 were similar across the quetiapine treatment groups, but were marginally higher in the lithium-treated group and lower in the placebo group. Mean change from baseline in SAS and BARS scores at week 8 were minimal in all treatment groups. The overall safety results did not alter the known risk-benefit profile of quetiapine.[37]

Given the observations in this study and the necessity for the monitoring of potential toxicity associated with lithium treatment,[38] these findings suggest that quetiapine treatment in patients with bipolar depression may generally provide greater benefits than lithium, an older, more conventional treatment.

Differences in patient numbers within the sample populations may have influenced the results for some outcome measures in this study. For example, although treatment differences for MADRS total score between placebo and quetiapine treatment in patients with bipolar I and II disorder were similar, this difference only reached significance for patients with bipolar I disorder, which may be explained by the fact that the number of patients with bipolar I disorder was almost twice as high as the number of patients with bipolar II disorder. Similarly, the magnitude of functional improvement (SDS and MOS-Cog) was similar for quetiapine and lithium, but the smaller sample population size may account for the nonsignificant results in lithium-treated patients.

In addition to quetiapine monotherapy, the atypical antipsychotic olanzapine (monotherapy or in combination with fluoxetine) has demonstrated efficacy in the treatment of bipolar depression.[16] In contrast, patients with bipolar I disorder experiencing a major depressive episode treated with aripiprazole monotherapy had no significant improvements over placebo treatment in 2 randomized, placebo-controlled studies.[39] It remains to be determined whether additional atypical antipsychotics are similarly efficacious as monotherapy in bipolar depression, although variability in the pharmacologic profiles of these agents implies differences in their clinical effectiveness. Indeed, it has been shown that the magnitude of effect (compared with placebo) for quetiapine monotherapy exceeds that for olanzapine monotherapy.[19,40]

Studies of other treatments for bipolar depression have not shown promising results. Patients in a depressive phase of bipolar I or II disorder who were receiving a mood stabilizer were randomly assigned to treatment with risperidone, paroxetine, or a combination of both. The results indicated that there were no differences between each of the 3 treatment groups and that the depressive effects of treatment were only modest.[41] Lamotrigine has also been shown not to be effective for the acute treatment of bipolar depression.[15] In contrast, the beneficial antidepressant effects of quetiapine may reflect a unique mechanism of action that involves direct and indirect pharmacologic actions mediated by quetiapine and its active metabolite, norquetiapine. The affinity of norquetiapine for the norepinephrine transporter (NET) and the consequent inhibition of norepinephrine uptake is one of the potential mechanisms that are postulated to underlie the observed antidepressant properties of quetiapine in patients with bipolar depression.[42] Currently, quetiapine is the only atypical antipsychotic approved as monotherapy by the US Food and Drug Administration for both phases of bipolar disorder.[43] In addition to its acute efficacy, 2 large clinical studies have also shown long-term maintenance of efficacy (up to 104 weeks) with quetiapine in combination with lithium or valproate in patients with bipolar I disorder.[44,45]

The burden of symptoms of depression on the clinical outcome of patients with bipolar disorder is a mounting concern. The results from the acute treatment phase of this large-scale study and the similarly designed EMBOLDEN II and BOLDER I and II studies have demonstrated the efficacy of quetiapine monotherapy for the treatment of bipolar depression. The improvements in symptoms of depression were evident within the first week of treatment and confirm previous findings from the BOLDER studies. Quetiapine was also associated with greater symptomatic improvements than lithium, one of the oldest and most established mood stabilizers. The findings from this study have considerable importance in view of the clear need for effective treatments for bipolar depression.

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Drug names: aripiprazole (Abilify), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), olanzapine-fluoxetine combination (Symbyax), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), zaleplon (Sonata and others), zolpidem (Ambien, Edluar, and others), zopiclone (Lunesta).
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National Institute of Mental Health, OREXIGEN Therapeutics, Pfizer, Sanofi-Synthelabo, Somaxon, Stanley Medical Research Institute, and Takeda and is an inventor on United States Patent No. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and, along with the patient's assignee, University of Cincinnati, Cincinnati, Ohio, has received payments from Johnson & Johnson, which has exclusive rights under the patent. **Dr Bauer** is a consultant to or member of the scientific advisory boards of and has received honoraria from Eli Lilly, Wyeth, Servier, GlaxoSmithKline, AstraZeneca, and Bristol-Myers Squibb. **Drs Chang** and **Brecher** are former employees of AstraZeneca. **Drs Olausson** and **Paulsson** are employees of AstraZeneca. **Dr Philips** reports no additional personal financial or other relationship relevant to the subject of this article.

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