A Double-Blind, Placebo-Controlled Study of Quetiapine and Paroxetine as Monotherapy in Adults With Bipolar Depression (EMBOLDEN II)

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Objective: The aim of this study was to evaluate the efficacy and tolerability of quetiapine and paroxetine monotherapy for major depression in bipolar disorder.

Method: 740 patients (478 bipolar I, 262 bipolar II) with major depressive episodes (*DSM-IV*) were randomly assigned to quetiapine 300 mg/d (n = 245), quetiapine 600 mg/d (n = 247), paroxetine 20 mg/d (n = 122), or placebo (n = 126) for 8 weeks. The primary end point was the change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score. The study was conducted from May 2005 to May 2007.

Results: Mean MADRS score change from baseline at 8 weeks was –16.19 for quetiapine 300 mg, –16.31 for quetiapine 600 mg, –13.76 for paroxetine, and –12.60 for placebo ($P < .001$ for both quetiapine doses, $P = .313$ for paroxetine, vs placebo). Quetiapine-treated (both doses), but not paroxetine-treated, patients showed significantly greater improvements ($P \leq .05$) in most secondary outcomes measures at week 8 versus the placebo group. Paroxetine significantly improved Hamilton Anxiety Rating Scale scores versus placebo ($P < .05$) but not MADRS or Hamilton Depression Rating Scale (HDRS) scores. Both quetiapine doses were associated with greater improvements than paroxetine for MADRS and HDRS scores. The most common adverse events were dry mouth, somnolence, sedation, and dizziness with quetiapine (both doses) and dry mouth, sedation, headache, insomnia, and nausea with paroxetine. The incidence of treatment-emergent mania/hypomania was lower with quetiapine compared with paroxetine and placebo.

Conclusions: Quetiapine (300 or 600 mg/d), but not paroxetine, was more effective than placebo for treating acute depressive episodes in bipolar I and II disorder. Quetiapine treatment was generally well tolerated.

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Neuropsychiatric disorders account for a large part of the global burden of disease.[1] Bipolar disorder, a long-term illness characterized by ≥ 1 episode of mania or hypomania usually alternating with recurring major depressive episodes, is an important contributor to this disease burden.[1,2] The estimated lifetime prevalence of bipolar I and II disorder is 1.0% and 1.1%, respectively,[3] although other studies have reported that the lifetime rate for bipolar I disorder may be as high as 3.3%, suggesting that the economic implications of this illness may have been previously underestimated.[4]

Screening studies have shown bipolar disorder to be particularly common in primary care practices, where patients usually present with depression.[5,6] Indeed, mounting research shows that depression dominates the course of bipolar disorder and accounts for the greater proportion of the associated disease burden, including higher rates of suicidality.[1,7–11] Suicide attempts in patients with bipolar disorder are often associated with up to 10-fold greater lethality, with a suicide mortality rate approximately 10 times higher than in the general population according to 1 study[12] and approximately 1% annually, 60 times higher than the annual international population rate of 0.015%, according to another.[10]

Despite the predominance of bipolar depression, guidelines for the treatment of acute depressive episodes in bipolar I and II disorder are not informed by a rich evidence base. Treatment guidelines published over the past 5 to 10 years have generally recommended the use of traditional mood stabilizers (eg, lithium, divalproex, carbamazepine, and lamotrigine) for acute episodes of depression, either alone or in combination with an antidepressant (eg, a selective serotonin reuptake inhibitor [SSRI] or bupropion).[2,13,14]

However, evidence regarding the efficacy and safety of antidepressants for bipolar depression remains unclear. A recent meta-analysis suggested that the combination of an antidepressant and mood stabilizer was effective in bipolar depression,[15] yet a prospective study, which was a part of the large-scale, multisite Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) clinical trial funded by the National Institutes of Health's National Institute of Mental Health, failed to identify any such advantage.[16] The potential risk of treatment-emergent hypomania or mania associated with the acute or long-term use of antidepressants has led some to discourage their use for bipolar depression,[17] but antidepressant monotherapy still remains common practice in some parts of the world, particularly for patients with bipolar II disorder. In the current clinical setting in the United States, for example, antidepressants are the most commonly prescribed monotherapy for patients with bipolar disorder, with approximately 50% of patients initiating treatment in this manner and persisting with treatment over the long term.[18]

More recent evidence has indicated that the atypical antipsychotics also have antidepressant effects, and treatment guidelines are adapting to reflect the possibility of managing bipolar depression with antipsychotics.[19–21] The combination of olanzapine and the SSRI fluoxetine was the first treatment to be approved specifically for the acute management of bipolar depression by the US Food and Drug Administration (FDA). The atypical antipsychotic quetiapine was the first agent to be licensed as monotherapy to treat depression associated with bipolar I and II disorder.[22] The FDA indication for quetiapine was granted on the basis of the pivotal BOLDER I and II (BipOLar DEpRession) trials.[23,24] Collectively, the BOLDER studies demonstrated that 2 doses of quetiapine monotherapy (300 mg and 600 mg given once daily) were significantly more effective than placebo against the depressive symptoms of bipolar disorder over 8 weeks, with no increased risk of treatment-emergent manic or hypomanic switches. Post BOLDER, there is now a need for comparative trials to evaluate quetiapine monotherapy among other widely used treatment options. This study, Efficacy of Monotherapy Seroquel in BipOLar DEpressioN II (EMBOLDEN II), is 1 of 2 large studies (EMBOLDEN I and EMBOLDEN II) 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 in patients with a most recent major depressive episode. The studies also included paroxetine (EMBOLDEN II) and lithium (EMBOLDEN I) comparator arms.[25] The active comparators were included in order to assess assay sensitivity (comparison vs placebo) and to provide data for assessing the risk-benefit ratio of quetiapine versus commonly used treatments for bipolar depression. Both EMBOLDEN studies also incorporated a 26- to 52-week placebo-controlled continuation treatment phase of quetiapine monotherapy that was designed to enable pooling of data. Results from the acute treatment phase of EMBOLDEN II are presented here. The selection of paroxetine as the active comparator in this study was based on previous controlled studies in bipolar depression.[26–28] Additionally, paroxetine is commonly used in clinical practice in the treatment of patients with bipolar depression and is thought to be associated with a significantly lower risk for switching to mania or mood instability than the tricyclic antidepressants and venlafaxine, and an only slightly higher risk than that associated with bupropion.[17,29]

METHOD

Study Design

This randomized, double-blind, parallel-group, placebo-controlled, multicenter study was conducted to evaluate the efficacy and safety of quetiapine and paroxetine, each as monotherapy, in the treatment of adults with bipolar depression over 8 weeks. The study was conducted in a total of 83 centers in the United States, EU member states, Turkey, Central and South America, South Africa, and Australia, between May 2005 and May 2007. The study was designed and conducted in line with the current amendment of the Declaration of Helsinki and International Conference on Harmonization (ICH)/Good Clinical Practice guidelines. A signed informed consent form approved by the relevant institutional review boards was obtained from all patients prior to participation.

Patients were randomly assigned to receive acute treatment with quetiapine (300 or 600 mg/d), paroxetine (20 mg/d), or placebo for 8 weeks. After the 8-week acute treatment phase, eligible patients, with Montgomery-Asberg Depression Rating Scale (MADRS)[30] and Young Mania Rating Scale (YMRS)[31] total scores ≤ 12, could enter a placebo-controlled continuation phase with quetiapine for 26 up to 52 weeks. The results of the continuation phase will be published separately.

Patients

Patients aged 18 years or older, with a documented clinical diagnosis of bipolar I or II disorder, most recent episode depressed, as defined by *DSM-IV*,[32] with or without a rapid-cycling course (≥ 4 episodes to ≤ 8 episodes per year), were eligible for inclusion in the study. Additional enrollment criteria included a 17-Item Hamilton Depression Rating Scale (HDRS)[33] score ≥ 20, an HDRS item 1 (depressed mood) score ≥ 2, and a YMRS score ≤ 12.

Patients with a *DSM-IV* diagnosis of an Axis I disorder other than bipolar disorder that was the primary focus of treatment within the 6 months prior to screening were excluded. Patients with a previously known lack of response to quetiapine or paroxetine therapy were also excluded. Additional exclusion criteria included a diagnosis of current episode of depression exceeding 12 months or less than 4 weeks in duration from enrollment, HDRS item 3 (suicide)

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score ≥ 3, more than 8 mood episodes 12 months prior to enrollment, substance dependence diagnosis (*DSM-IV*) or substance use (with the exception of nicotine) within 12 months prior to screening, clinically significant comorbid diseases, and the use of drugs that induce or inhibit the hepatic metabolizing cytochrome P450 3A4 enzymes in the 14 days prior to enrollment. Female patients who were pregnant, lactating, or of childbearing potential and not using a reliable method of contraception were also excluded.

Study Medication

After a washout phase that lasted for 5 to 28 days, patients were randomly assigned, in a 2:2:1:1 ratio, to quetiapine 300 mg/d, quetiapine 600 mg/d, paroxetine 20 mg/d, or placebo treatment groups once daily at bedtime. The washout period generally lasted for 5 days, although the duration was dependent on the type of medication being discontinued; for example, the use of fluoxetine was not permitted within 28 days of randomization, and extended-release risperidone, irreversible monoamine oxidase inhibitors, and tapering of lithium dose were not permitted within 14 days of randomization. The randomization was stratified by bipolar diagnosis (bipolar I or II disorder) and country, using an interactive response system. 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.

Quetiapine was initiated at 50 mg/d and titrated to reach a dose of 300 mg/d by day 4 and 600 mg/d by day 8 (in the 600 mg/d treatment group).

Concomitant Medication

Patients were allowed to continue taking previous medications for nonpsychiatric medical illnesses throughout the study. Concomitant treatment with other psychoactive drugs was prohibited except for lorazepam (1–3 mg/d), zolpidem tartrate (≤ 10 mg/d), zaleplon (≤ 20 mg/d), zopiclone (≤ 7.5 mg/d), and chloral hydrate (≤ 1 g/d), which were permitted during the first 3 weeks of the study. Anticholinergics were permitted to treat extrapyramidal symptoms (EPS), but prophylactic use was prohibited.

Efficacy Evaluations

The primary efficacy measure was the change from baseline to week 8 in MADRS total score. Secondary efficacy measures included response (defined as ≥ 50% decrease from baseline in MADRS total score), remission (defined as MADRS total score ≤ 12 at week 8), and change from baseline to week 8 in MADRS individual item scores, MADRS item 10 (suicidal thoughts) score, HDRS total score, HDRS item 1 (depressed mood) score, Clinical Global Impressions-Bipolar-Severity of Illness (CGI-BP-S)[34] score, Clinical Global Impressions-Bipolar-Change (CGI-BP-C)[34] score, and Hamilton Anxiety Rating Scale (HARS)[35] score. The patient-reported Sheehan Disability Scale (SDS)[36] and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[37] were also included as secondary efficacy variables.

Safety and Tolerability Evaluations

The incidence, severity, and withdrawals attributed to adverse events (AEs) were recorded at each visit. Adverse events were classified according to Medical Dictionary for Regulatory Activities (MedDRA) terminology. Additional safety measures included the proportion of patients meeting criteria for treatment-emergent mania or hypomania (YMRS score ≥ 16 on 2 consecutive visits or at final assessment or treatment-emergent mania/hypomania reported as an AE) and the proportion of patients with treatment-emergent suicidal ideation (HDRS item 3 [suicide] score ≥ 3 or an AE of suicidality, suicidal ideation, suicide attempts, or suicide completion).

Safety end points also included vital signs and laboratory test results, weight and body mass index (BMI), electrocardiogram (ECG), and physical examination results. EPS were evaluated using the Simpson-Angus Scale (SAS),[38] the Barnes Akathisia Rating Scale (BARS),[39] and the Abnormal Involuntary Movement Scale (AIMS).[40] Sexual functioning was assessed using the Changes in Sexual Functioning Questionnaire.[41]

Statistical Analysis

Efficacy analyses were based on the intent-to-treat (ITT) population, which comprised patients who had received at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment. Last-observation-carried-forward (LOCF) methodology was used to deal with missing data from patient dropout in the efficacy analyses. The primary outcome variable, the change from baseline to week 8 in MADRS total score, was analyzed using a linear mixed model with fixed effects for treatment and bipolar diagnosis strata; baseline MADRS total score was included as a covariate, and country was included as a random effect. The comparison of interest was the difference between each quetiapine dose and placebo, and adjustments for multiple comparisons used a Hochberg approach. Adjustments for multiple comparisons were not made for the comparison between paroxetine and placebo.

Secondary analyses utilized the same linear model as for the primary analysis for variable changes, from baseline to week 8, in HDRS, HDRS item 1, HARS, and CGI-BP-S scales. The variable CGI-BP-C was analyzed using a similar linear model. In addition, the dichotomous variables responders (≥ 50% decrease from baseline in MADRS total

Table 1. Baseline Demographics and Disease Characteristics (ITT population)

Characteristic	Quetiapine 300 mg/d (n = 229)	Quetiapine 600 mg/d (n = 232)	Paroxetine 20 mg/d (n = 118)	Placebo (n = 121)
Gender, %				
Male	38.4	39.2	36.4	33.1
Female	61.6	60.8	63.6	66.9
Age, mean, y	38.4	38.5	39.3	38.7
DSM-IV diagnosis, %				
Bipolar I disorder	64.6	64.7	62.7	62.8
Bipolar II disorder	35.4	35.3	37.3	37.2
Mood episodes over past year, %				
< 4	79.9	84.9	79.7	80.2
≥ 4 (rapid cycling)	20.1	15.1	20.3	19.8
MADRS score, mean	27.1	26.5	27.3	27.2
HDRS score, mean	24.2	24.2	24.1	24.2
HARS score, mean	18.6	18.5	18.8	18.6
YMRS score, mean	5.5	5.9	5.5	5.9

Abbreviations: 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.

score), remitters (MADRS total score ≤ 12), and CGI-BP-C response (CGI-BP-C overall illness score ≤ 2) were analyzed using the 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.

Safety analyses were based on all patients who received at least 1 dose of study medication (safety population). For safety analyses for which the change from baseline was the primary focus, only patients with both baseline and postbaseline data were included. Descriptive statistics of incidence rates were used to evaluate AEs (including serious AES [SAEs], AEs leading to withdrawal, and deaths if any) and reasons for study withdrawal. Statistical analysis of safety end points was not planned in the study protocol.

The study was powered at 87% power to detect a 4-point 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).

RESULTS

Patients and Disposition

A total of 1,076 patients were screened, and 740 patients (478 bipolar I, 262 bipolar II) were randomized. Of these, 732 patients received at least 1 dose of study medication and were included in the safety population. A total of 700 patients were included in the ITT population and received quetiapine 300 mg/d (n = 229), quetiapine 600 mg/d (n = 232), paroxetine 20 mg/d (n = 118), or placebo (n = 121). All treatment groups (ITT population) were comparable in terms of age, bipolar diagnosis, and disease severity scores at baseline (Table 1). The proportion of patients using psychotropic medications prior to randomization was similar between treatment groups (30.5%, 29.5%, 27.3%, and 26.6% for quetiapine 300 mg/d, quetiapine 600 mg/d, paroxetine, and placebo groups, respectively). Similar proportions of patients in each treatment group had previously used antidepressants (16.5%, 17.2%, 14.0%, and 16.1%, respectively), lamotrigine (1.6%, 2.0%, 1.7%, and 1.6%), or lithium (1.6%, 3.3%, 1.7%, and 1.6%).

Study completion rates were similar between treatment groups (65.3%, 64.4%, 62.3%, and 60.3% for quetiapine 300 mg/d, quetiapine 600 mg/d, paroxetine 20 mg/d, and placebo, respectively). Patient disposition is shown in Figure 1.

Efficacy Variables

MADRS. Quetiapine (300 and 600 mg/d) was significantly more effective than placebo in reducing the MADRS total score from week 2 ($P < .05$) onward, and these improvements were maintained to the end of the acute treatment phase at week 8 ($P < .001$; Figure 2 and Table 2). Paroxetine did not result in statistically significant improvement in MADRS total score compared with placebo at any time point during the study (week 8, $P = .313$). Both doses of quetiapine were associated with significantly greater improvements over paroxetine in MADRS total score at week 8 (–2·43, $P = .017$ and –2·55, $P = .012$ for 300 and 600 mg/d, respectively).

Compared with placebo, quetiapine 600 mg/d demonstrated significant improvement in all MADRS individual items with the exception of lassitude ($P < .05$; Figure 3). Quetiapine 300 mg/d demonstrated significant improvement over placebo in all MADRS items except reported sadness, lassitude, and inability to feel ($P < .05$). At 8 weeks, both doses of quetiapine were associated with a significantly greater reduction in suicidal thoughts (MADRS item 10) than placebo ($P < .05$). Treatment with paroxetine did not result in significantly greater reductions than placebo in any individual MADRS item scores, including suicidal thoughts.

A significantly greater proportion of quetiapine-treated patients were classified as MADRS responders at week 8 (66.8% and 67.2% for quetiapine 300 and 600 mg/d) than placebo-treated patients (52.9%; $P = .01$ and $P < .01$, respectively), with NNTs of 7 for both quetiapine 300 mg/d and 600 mg/d. The proportion of paroxetine-treated patients meeting response criteria (55.1%) was not significantly different from placebo ($P = .735$; NNT = 46).

Remission was achieved at week 8 in a significantly greater proportion of patients receiving quetiapine 600 mg/d (68.5%; $P < .05$; NNT = 8) compared with placebo (55.4%). The rates of remission among patients receiving quetiapine 300 mg/d and paroxetine did not differ significantly from placebo (64.6% [$P = .081$] and 56.8% [$P = .828$], NNTs of 11 and 71, for quetiapine 300 mg/d and paroxetine, respectively). Of those patients meeting remission criteria, the following proportions had MADRS total scores < 24 at baseline: 47.8% of the placebo group; 35.1% and 42.1% of

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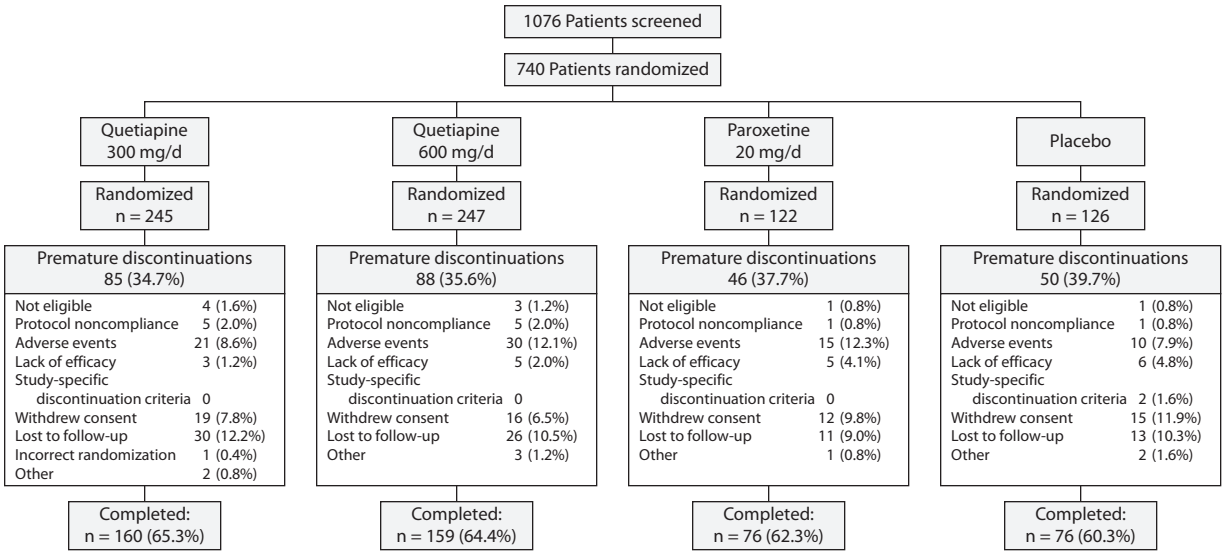
Figure 1. Patient Disposition



the quetiapine 300 mg/d and 600 mg/d groups, respectively; and 38.8% of the paroxetine group.

Bipolar I and II subgroups. Both quetiapine doses were associated with significant improvements over placebo in 8-week MADRS total score, in the bipolar I and II subgroups ($P < .05$; Figure 2B and 2C). In the bipolar I subgroup, the mean change in MADRS total score from baseline at week 8 was –16.17 in the quetiapine 300 mg/d group, –16.43 in the quetiapine 600 mg/d group, and –14.87 in the paroxetine 20 mg/d group, compared with –13.39 in the placebo group. In the bipolar II subgroup, the mean change from baseline at week 8 was –16.50 in the quetiapine 300 mg/d group, –16.33 in the quetiapine 600 mg/d, and –11.90 in the paroxetine 20 mg/d group, compared with –11.53 in the placebo group. Paroxetine-treated patients did not show a significant improvement over placebo at week 8 in either the bipolar I or II subgroups.

Rapid- and non-rapid-cycling course. Among the relatively few patients with a rapid-cycling disease course, the change in MADRS total score from baseline to end point was generally uniform across treatment groups (–15.86 [n = 46], –16.62 [n = 35], –16.67 [n = 24], –14.37 [n = 24] for quetiapine 300 mg/d, quetiapine 600 mg/d, placebo, and paroxetine groups, respectively). The differences between the active treatment groups and placebo were not statistically significant in this small patient subgroup.

The change from baseline in MADRS total score for non-rapid-cycling patients treated with quetiapine 300 mg/d, quetiapine 600 mg/d, placebo, and paroxetine was –16.29 (n = 183), –16.08 (n = 197), –11.66 (n = 97), and –13.50 (n = 94), respectively. Patients with a non-rapid-cycling disease course treated with either dose of quetiapine showed significantly greater ($P < .001$) improvement in MADRS score at week 8 than patients treated with placebo. The difference between paroxetine- and placebo-treated patients was not significant.

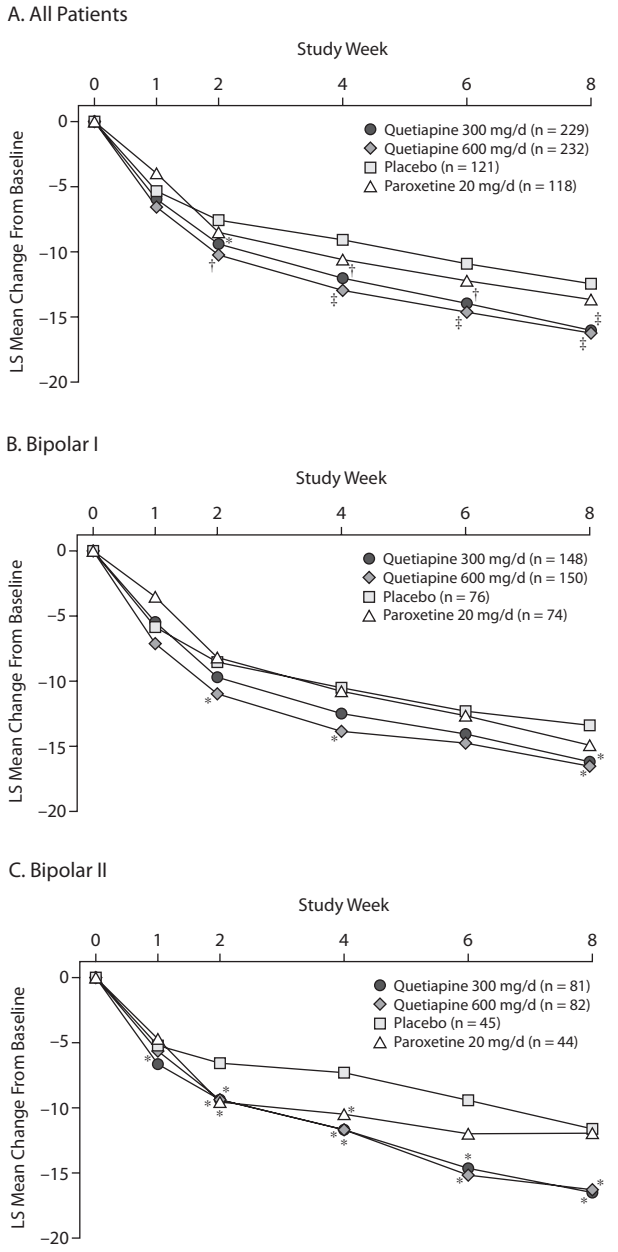
HDRS. Quetiapine (300 and 600 mg/d) demonstrated significantly greater improvement over placebo in HDRS total score as early as week 1 (600 mg/d; $P < .001$) or week 2 (300 mg/d; $P < .01$), which was sustained to week 8 ($P < .001$ for both doses; Table 2). Treatment with paroxetine did not result in a significant improvement over placebo. Both quetiapine doses showed improvement over paroxetine in HDRS total score at week 8 (–2.15, $P = .010$, and –2.56, $P = .002$, for quetiapine 300 and 600 mg/d, respectively).

Quetiapine-treated patients (300 and 600 mg/d) experienced greater mean reductions in HDRS item 1 (depressed mood) scores than those treated with placebo or paroxetine (Table 2). The mean change in HDRS item 1 score among paroxetine-treated patients was not significantly different from placebo.

HARS. A significant decrease in mean HARS total score was apparent from week 2 onward for quetiapine 600 mg/d ($P < .05$) and week 3 onward for quetiapine 300 mg/d and paroxetine ($P < .001$ and $P < .05$, respectively; Table 2).

CGI-BP-S. Significantly greater improvement ($P < .05$) on the CGI-BP-S scale was noted following quetiapine treatment (300 and 600 mg/d) compared with placebo. This improvement was observed as early as week 1 for quetiapine 600 mg/d ($P < .05$) and week 2 for quetiapine 300 mg/d ($P < .05$) and was largely maintained until the end of the acute treatment phase (week 8; Table 2). Treatment with paroxetine did not result in a significant improvement over placebo (LOCF) at any assessment. A significantly

Figure 2. Mean Change in MADRS Total Score (ITT, LOCF)



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

Table 2. Mean Change in Efficacy Measures at Last Assessment (ITT, LOCF)

Efficacy Assessment	Baseline Score, Mean (SE)	LS Mean Change at Last Assessment (week 8)	*P* Value (vs placebo)
MADRS			
Quetiapine 300 mg/d	27.1 (0.49)	−16.19	<.001
Quetiapine 600 mg/d	26.5 (0.51)	−16.31	<.001
Paroxetine 20 mg/d	27.3 (0.64)	−13.76	.313
Placebo	27.2 (0.71)	−12.60	
MADRS item 10			
Quetiapine 300 mg/d	1.1 (0.08)	−0.71	.035
Quetiapine 600 mg/d	1.0 (0.07)	−0.76	.010
Paroxetine 20 mg/d	1.0 (0.09)	−0.55	.759
Placebo	1.3 (0.11)	−0.52	
HDRS			
Quetiapine 300 mg/d	24.2 (0.24)	−14.68	<.001
Quetiapine 600 mg/d	24.2 (0.23)	−15.09	<.001
Paroxetine 20 mg/d	24.1 (0.30)	−12.53	.240
Placebo	24.2 (0.30)	−11.42	
HDRS item 1			
Quetiapine 300 mg/d	2.9 (0.04)	−1.66	<.01
Quetiapine 600 mg/d	2.8 (0.04)	−1.67	<.01
Paroxetine 20 mg/d	2.8 (0.05)	−1.51	.196
Placebo	2.9 (0.05)	−1.33	
HARS			
Quetiapine 300 mg/d	18.6 (0.41)	−10.61	<.001
Quetiapine 600 mg/d	18.5 (0.38)	−10.19	<.001
Paroxetine 20 mg/d	18.8 (0.54)	−9.15	.033
Placebo	18.6 (0.60)	−7.32	
CGI-BP-S			
Quetiapine 300 mg/d	4.2 (0.05)	−1.67	.012
Quetiapine 600 mg/d	4.2 (0.05)	−1.65	.018
Paroxetine 20 mg/d	4.2 (0.07)	−1.44	.478
Placebo	4.3 (0.08)	−1.33	
Q-LES-Q			
Quetiapine 300 mg/d	36.9 (0.63)	8.75	.197
Quetiapine 600 mg/d	36.7 (0.59)	8.96	.139
Paroxetine 20 mg/d	37.0 (0.86)	7.96	.604
Placebo	37.0 (0.83)	7.28	
SDS			
Quetiapine 300 mg/d	17.8 (0.51)	−6.97	.291
Quetiapine 600 mg/d	18.3 (0.50)	−6.66	.471
Paroxetine 20 mg/d	19.4 (0.67)	−6.04	.969
Placebo	17.6 (0.72)	−6.00	

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, LOCF = last observation carried forward, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SDS = Sheehan Disability Scale.

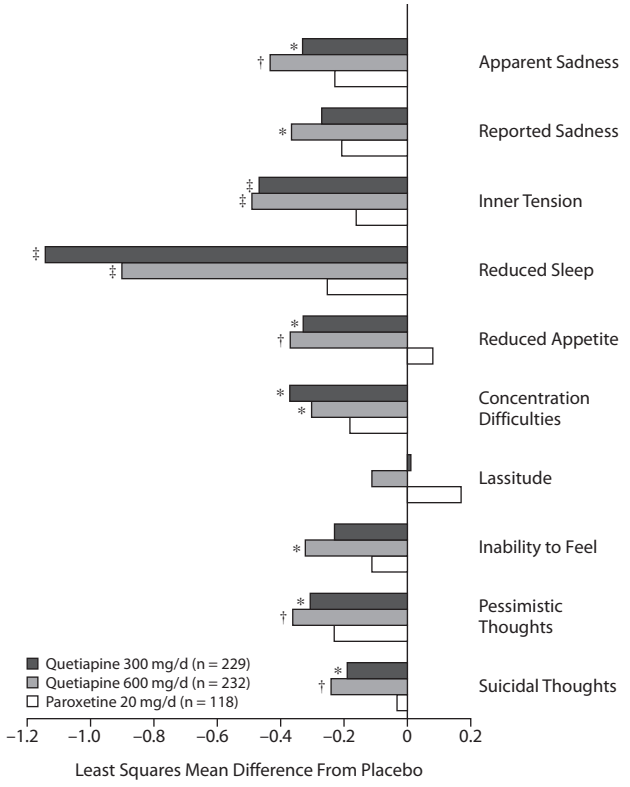
greater number of patients were rated as "much improved" or "very much improved" on the CGI-BP-C scale at week 8 in the quetiapine 300 mg/d group (53.3%) and the quetiapine 600 mg/d group (53.4%; $P < .05$ for both quetiapine doses vs placebo) than in the placebo group (40.5%). The comparison between the paroxetine and the placebo treatment groups was not statistically significant (49.2% vs 40.5%; $P = .179$).

Functioning and quality of life. Similar functional improvement, determined by reduction from baseline in SDS scores, was noted in all groups following 8 weeks of treatment (Table 2). All groups showed an improvement (increase) in Q-LES-Q scores, but no treatment showed statistical significance over placebo at study end point (Table 2). Changes in sexual functioning associated with the active treatment groups did not differ significantly from placebo at week 8.

Safety and Tolerability

Adverse events leading to treatment discontinuation were reported in 9.1% (n = 22) of the quetiapine 300 mg/d group, 12.3% (n = 30) of the quetiapine 600 mg/d group, 13.2%

Figure 3. Mean Change From Baseline in MADRS Individual Item Scores (ITT, LOCF)



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

(n = 16) of the paroxetine group, and 8.1% (n = 10) of the placebo group (safety population). The incidence of serious AEs was lowest among patients receiving quetiapine 300 mg/d (0.4%). Patients treated with paroxetine displayed the highest incidence of serious AEs (7.4%), and these included depression (1 patient [0.8%]), atrial fibrillation (1 patient [0.8%]), bipolar I disorder (2 patients [1.7%]), cellulitis (1 patient [0.8%]), hypomania (1 patient [0.8%]), mania (2 patients [1.7%]), and stress (1 patient [0.8%]). Overall, depression was among the most common serious AEs and was reported in 1 patient in each of the quetiapine 300 mg/d (0.4%), paroxetine (0.8%), and placebo (0.8%) groups and 3 patients in the quetiapine 600 mg/d group (1.2%). Mania was reported as a serious AE in 3 patients receiving quetiapine 600 mg/d (1.2%), 2 patients receiving paroxetine (1.7%), and 1 patient receiving placebo (0.8%). The proportion of patients reporting any AE was similar between treatment groups (Table 3). The most common AEs among quetiapine-treated patients included dry mouth, somnolence, sedation, and dizziness (Table 3). The most common AEs among paroxetine-treated patients included dry mouth, sedation, headache, nausea, and insomnia.

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

Adverse Event	Quetiapine 300 mg/d (n = 243)	Quetiapine 600 mg/d (n = 244)	Paroxetine 20 mg/d (n = 121)	Placebo (n = 124)
Any adverse event	160 (65.8)	171 (70.1)	84 (69.4)	79 (62.9)
Serious adverse event	1 (0.4)	9 (3.7)	9 (7.4)	4 (3.2)
Dry mouth	53 (21.8)	63 (25.8)	12 (9.9)	7 (5.6)
Somnolence	46 (18.9)	43 (17.6)	7 (5.8)	10 (8.1)
Sedation	31 (12.8)	39 (16.0)	10 (8.3)	6 (4.8)
Dizziness	28 (11.5)	34 (13.9)	8 (6.6)	7 (5.6)
Headache	24 (9.9)	24 (9.8)	19 (15.7)	16 (12.9)
Fatigue	16 (6.6)	19 (7.8)	4 (3.3)	4 (3.2)
Constipation	14 (5.8)	22 (9.0)	6 (5.0)	2 (1.6)
Nausea	14 (5.8)	22 (9.0)	15 (12.4)	7 (5.6)
Dyspepsia	8 (3.3)	14 (5.7)	2 (1.7)	3 (2.4)
Increased appetite	8 (3.3)	13 (5.3)	3 (2.5)	3 (2.4)
Insomnia	5 (2.1)	5 (2.0)	16 (13.2)	13 (10.5)
Diarrhea	4 (1.6)	7 (2.9)	8 (6.6)	5 (4.0)
Decreased appetite	2 (0.8)	2 (0.8)	6 (5.0)	0
Anxiety	1 (0.4)	6 (2.5)	6 (5.0)	7 (5.6)

[a]Values shown as n (%).
[b]Patients with multiple events in the same category are counted only once in that category.

Treatment-emergent mania. The incidence of treatment-emergent mania or hypomania (reported as an AE or as a YMRS score ≥ 16 on 2 consecutive visits) was numerically lower in the quetiapine groups compared with the paroxetine and placebo groups (2.1% with quetiapine 300 mg/d, 4.1% with 600 mg/d, 10.7% with paroxetine 20 mg/d, and 8.9% with placebo).

Suicidality. The incidence of treatment-emergent suicidal ideation (proportion of patients with HDRS item 3 [suicide] score ≥ 3 or an AE of suicidality, suicidal ideation, suicide attempt, or suicide completion) was similar across all treatment groups (2.9%, 2.0%, 3.3%, and 4.0%, for quetiapine 300 mg/d, quetiapine 600 mg/d, paroxetine, and placebo, respectively). As mentioned previously, both doses of quetiapine were associated with a significantly greater reduction in suicidal thoughts (MADRS item 10) than placebo ($P < .05$) at 8 weeks.

EPS. AEs potentially related to EPS (including the MedDRA terms *akathisia, restlessness, tremor, extrapyramidal disorder, dystonia, cogwheel rigidity, dyskinesia, hypokinesia,* and *movement disorder*) were reported for 8.2% of the patients in the quetiapine 300 mg/d group, 9.8% of the patients in the quetiapine 600 mg/d group, 2.4% of the patients in the placebo group, and 4.1% of patients in the paroxetine group. Mean changes in BARS scores were similar across treatment groups following 8 weeks of treatment: –0.1 in the quetiapine (both doses) and 0 in the placebo and the paroxetine groups. The proportion of patients with "worsened" SAS total score was similar across treatment groups: 9.3% (n = 21) with quetiapine 300 mg/d, 8.6% (n = 20) with 600 mg/d, 12.0% (n = 14) with paroxetine 20 mg/d, and 14.3% (n = 17) with placebo.

Weight. Following 8 weeks of treatment, mean weight gain from baseline was greater among patients treated with

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

	Baseline		End of Treatment		Change From Baseline		*P* Value	Proportion of Patients With Clinically Relevant Changes[a]	
Parameter and Treatment	Mean	SE	Mean	SE	Mean	SE	(vs Placebo)	n[b]	n (%)
Weight, kg									
Quetiapine 300 mg/d	81.5	1.67	82.6	1.67	1.1	0.21	.107	177	16 (9.0)
Quetiapine 600 mg/d	81.4	1.40	83.1	1.40	1.7	0.23	< .001	194	22 (11.3)
Paroxetine	84.7	2.40	84.4	2.39	−0.3	0.29	.111	90	3 (3.3)
Placebo	79.6	2.18	80.1	2.22	0.5	0.27	…	97	4 (4.1)
BMI, kg/m^2									
Quetiapine 300 mg/d	28.8	0.59	29.2	0.60	0.4	0.07	.078	…	…
Quetiapine 600 mg/d	28.9	0.46	29.5	0.47	0.6	0.08	< .001	…	…
Paroxetine	30.1	0.77	30.0	0.77	−0.1	0.10	.111	…	…
Placebo	28.7	0.76	28.9	0.77	0.2	0.09	…	…	…
HbA_{1c}, %									
Quetiapine 300 mg/d	5.50	0.04	5.65	0.06	0.15	0.03	.009	165	2 (1.2)
Quetiapine 600 mg/d	5.52	0.03	5.61	0.04	0.09	0.02	.311	181	1 (0.6)
Paroxetine	5.39	0.06	5.50	0.04	0.11	0.03	.189	89	0
Placebo	5.56	0.06	5.61	0.06	0.04	0.03	…	93	0
Glucose, mg/dL									
Quetiapine 300 mg/d	91.07	1.22	95.70	2.60	4.63	2.20	.373	125	7 (5.6)
Quetiapine 600 mg/d	91.53	1.46	94.72	1.34	3.18	1.61	.670	134	4 (3.0)
Paroxetine	89.53	1.33	91.09	1.89	1.57	1.69	.668	69	3 (4.3)
Placebo	89.60	1.47	92.38	1.65	2.78	1.20	…	70	1 (1.4)
Insulin, pmol/L									
Quetiapine 300 mg/d	95.52	7.24	125.96	11.11	30.45	10.61	.690	…	…
Quetiapine 600 mg/d	98.15	6.60	157.37	18.10	59.22	15.76	.345	…	…
Paroxetine	94.31	8.11	109.00	10.24	14.69	9.97	.302	…	…
Placebo	107.84	18.66	148.03	29.05	40.20	19.20	…	…	…
Triglycerides, mg/dL									
Quetiapine 300 mg/d	144.58	7.86	165.52	10.73	20.94	7.44	.738	134	19 (14.2)
Quetiapine 600 mg/d	145.15	7.72	165.45	9.30	20.30	5.79	.784	150	22 (14.7)
Paroxetine	149.74	12.22	156.13	11.29	6.39	10.96	.440	72	6 (8.3)
Placebo	142.81	10.27	160.22	14.86	17.42	9.23	…	77	10 (13.0)
Total cholesterol (mg/dL)									
Quetiapine 300 mg/d	189.44	3.37	186.11	3.24	−3.33	2.30	.124	148	6 (4.1)
Quetiapine 600 mg/d	194.27	3.05	194.63	3.22	0.36	2.56	.800	159	13 (8.2)
Paroxetine	196.90	5.10	193.95	5.21	−2.95	3.80	.421	72	4 (5.6)
Placebo	188.09	4.32	191.05	4.35	2.96	2.74	…	84	3 (3.6)
HDL cholesterol (mg/dL)									
Quetiapine 300 mg/d	52.51	1.16	50.81	1.13	−1.71	0.65	.108	130	11 (8.5)
Quetiapine 600 mg/d	51.57	1.08	50.43	1.02	−1.13	0.68	.212	142	14 (9.9)
Paroxetine	52.49	1.64	53.28	1.90	0.80	1.25	.601	70	11 (15.7)
Placebo	51.45	1.27	51.67	1.36	0.23	0.81	…	75	3 (4.0)
LDL cholesterol, mg/dL									
Quetiapine 300 mg/d	108.54	2.93	104.11	2.80	−4.43	2.08	.205	153	7 (4.6)
Quetiapine 600 mg/d	112.73	2.64	111.36	2.75	−1.37	2.21	.998	165	13 (7.9)
Paroxetine	114.96	4.16	110.01	4.74	−4.94	3.31	.439	75	3 (4.0)
Placebo	107.27	3.46	107.42	3.40	0.15	2.22	…	86	3 (3.5)
Prolactin, µg/L									
Quetiapine 300 mg/d	10.81	0.62	10.65	1.03	−0.15	1.12	.616	M: 68, F: 94	M: 1 (1.5), F: 5 (5.3)
Quetiapine 600 mg/d	11.91	1.12	10.48	0.67	−1.43	0.78	.907	M: 65, F: 109	M: 2 (3.1), F: 1 (0.9)
Paroxetine	12.83	2.30	12.77	1.76	−0.06	0.99	.206	M: 34, F: 50	M: 0, F: 3 (6.0)
Placebo	12.27	1.34	10.83	0.98	−1.44	1.08	…	M: 28, F: 59	M: 0, F: 2 (3.4)

[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, and 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.

quetiapine (300 and 600 mg/d) than those receiving placebo or paroxetine (Table 4). The proportion of patients with weight increase (≥ 7%) was higher in both quetiapine groups compared with the paroxetine and placebo groups (9.0%, 11.3%, 3.3%, and 4.1% for quetiapine 300 mg/d, quetiapine 600 mg/d, paroxetine, and placebo groups, respectively; *P* = NS for all treatment groups vs placebo).

Laboratory parameters. Mean changes in laboratory parameters over 8 weeks of treatment and the proportion of patients demonstrating clinically relevant changes in lipid and glucose variables are presented in Table 4. Higher mean changes in insulin levels from baseline to last assessment were observed among patients in the quetiapine (both doses) and placebo groups compared with the paroxetine

group (Table 4). Similar mean increases in triglyceride levels were reported over the course of treatment for the quetiapine (both doses) and placebo groups, compared with a lower relative change in the paroxetine group. Treatment with either dose of quetiapine was associated with a reduction in high-density lipoprotein cholesterol, compared with an increase following treatment with paroxetine or placebo. All active treatments were associated with a reduction or a negligible increase in low-density lipoprotein cholesterol and total cholesterol (Table 4).

DISCUSSION

EMBOLDEN II, and the similarly designed EMBOLDEN I study in which lithium was the active comparator,[25] represent 2 of the largest placebo-controlled studies of bipolar depression to date in patients with bipolar I and II disorder. Here, the EMBOLDEN II study demonstrates the efficacy of quetiapine as monotherapy in the treatment of acute major depressive episodes. Quetiapine, at doses of 300 and 600 mg/d, was significantly more effective than placebo in reducing the symptoms of bipolar depression, as assessed by the change from baseline in MADRS total score (the primary end point). Quetiapine showed significant improvement compared with placebo on 7 and 9 of the 10 MADRS individual items (for quetiapine 300 mg/d and quetiapine 600 mg/d, respectively). The increased effectiveness of quetiapine over placebo was evident from week 2 onward on the MADRS (and as early as week 1 on the HDRS and CGI-BP scale with quetiapine 600 mg/d) and lasted throughout the 8-week trial.

These findings confirm the acute antidepressant effects of quetiapine that were previously reported in the BOLDER studies, in which significant improvements associated with quetiapine treatment were reported from week 1.[23,24] The fixed doses of quetiapine used in this study were consistent with the BOLDER studies and thus permitted direct between-study comparisons that would not have been possible if a flexible regimen had been followed.

Collectively, the EMBOLDEN and BOLDER trials provide confirmation of the efficacy of quetiapine in acute bipolar depression and represent 4 of the largest placebo-controlled studies to evaluate the efficacy of quetiapine monotherapy.[23–25] This consistency of effect is in contrast to that observed with other acute bipolar depression treatment options, including lamotrigine and aripiprazole.[42,43] The differentiating factor for quetiapine may be its mechanism of action, which may involve a combination of direct and indirect effects mediated by quetiapine and its active metabolite, norquetiapine. The affinity of norquetiapine for the norepinephrine transporter, and its ability to inhibit norepinephrine reuptake, represents one of a number of potential antidepressant mechanisms.[44]

That the differentiation of both doses of quetiapine from placebo was statistically significant, despite a placebo response rate of 52.9%, is testament to its robust clinical efficacy. The placebo response rate in the current study, although high, is largely consistent with previous clinical studies in bipolar depression in which placebo response rates of 29%–50% were observed for lamotrigine (5 trials) and 39%–44% for aripiprazole (2 trials).[42,43] These data highlight the variability that is seemingly inherent in studies of this type. The similarly variable and consistently high placebo response rates observed in clinical studies in major depression range from 13%–52%[45] and 30%–40%, with some studies reporting placebo response rates as high as 70%.[46] Additionally, we cannot discount the impact of investigator expectation on the placebo response rate observed in the current study, given that EMBOLDEN follows the highly successful BOLDER trials. Placebo response rates in BOLDER I and II were 36.1% and 44.7%, respectively.[23,24]

In the current study, the rates of response and remission observed for quetiapine 600 mg/d were of a similar magnitude (67.2% and 68.5% for response and remission, respectively). This can perhaps be attributed to the baseline MADRS total score of 26.5 in the quetiapine 600 mg/d group. A 50% reduction in MADRS total score not only satisfies response criteria but also is close to remission criteria (MADRS total score ≤ 12), thereby accounting for the similar percentage values.

Although numerical improvements were observed, neither active treatment in the current study showed significant differentiation from placebo in terms of the change in functioning or quality of life over time. This finding is in contrast to the BOLDER studies, in which quetiapine was associated with significant improvements in quality of life and functioning ($P < .05$).[23,24] This inconsistency may at least partly relate to the application of more generalized quality of life assessment tools to what is a highly unique psychiatric condition. The need for a quality of life instrument that is tailored specifically toward the complexities of bipolar disorder has been discussed previously.[47]

Paroxetine was generally not associated with significant improvements in efficacy measures compared with placebo, with the exception of a significant improvement in HARS score. The improvements in selected outcome variables associated with quetiapine, including MADRS and HDRS total scores, were greater than those associated with paroxetine. Moreover, patients treated with quetiapine (300 and 600 mg/d) showed significant improvement compared with paroxetine on MADRS items 3 (inner tension), 4 (reduced sleep), and 5 (reduced appetite), and significant improvement on MADRS item 10 (suicidal thoughts) was noted with quetiapine 600 mg/d versus paroxetine. Although 20 mg/d is the recommended starting dose of paroxetine for patients with depression and is within the prescribing limit for depression, it is possible that paroxetine may have demonstrated a more favorable efficacy profile if higher doses had been used; however, the safety profile would likely have been compromised at higher doses. Additional studies

using higher doses of paroxetine would be helpful. It is also important to note that the number of patients enrolled in the quetiapine groups was almost twice that in the paroxetine group, and, as such, the paroxetine group may have been less powered to detect differences from placebo compared with the quetiapine groups.

The usefulness of treating bipolar depression with antidepressants has always been a topic of clinical discussion, and the general lack of antidepressant efficacy observed in the current study may fuel the ongoing debate, at least as far as paroxetine is concerned. Paroxetine was selected as the active comparator on the basis of its use in previous controlled studies in bipolar depression[26–28] and its frequent clinical application in patients with bipolar depression. In addition, the propensity for switching to mania or mood instability with paroxetine is thought to be significantly lower than that associated with the tricyclic antidepressants[29] and venlafaxine.[17,48] In the current study, the incidence of treatment-emergent mania or hypomania observed with both doses of quetiapine was lower than that reported with placebo and paroxetine alike. This trend is consistent with that reported in the BOLDER studies, in which quetiapine was associated with lower or similar rates of treatment-emergent mania compared with placebo.[23,24] Interestingly, in the EMBOLDEN I study, while rates of mania were consistently low across all treatment groups, the lowest rates were associated with placebo (0.8%) rather than with quetiapine (2.2% and 4.2% with quetiapine 300 and 600 mg/d, respectively) or lithium (4.2%).[25]

The safety and tolerability profile of quetiapine observed in the current study was generally consistent with that reported in the BOLDER trials.[23,24] Despite the high rates of suicidality among patients with bipolar disorder, reported in the literature,[49] the rate of suicidal ideation associated with quetiapine treatment was low in the current study. All patients were closely monitored for increased suicidal thinking or behavior, particularly during the early phases of treatment, in accordance with FDA guidance. The incidence of treatment-emergent suicidal ideation associated with quetiapine was low and comparable to that seen following treatment with placebo or paroxetine. It should be noted, however, that the intentional exclusion of patients with serious suicidal risk was a noted limitation of the study design that precluded the evaluation of efficacy and tolerability in this high-risk, difficult-to-treat patient subgroup.

Also consistent with the BOLDER trials were the findings of weight gain and changes in glucose parameters among patients treated with quetiapine in the current study, although only the 1.7-kg weight increase observed for quetiapine 600 mg/d was significant compared with the 0.5-kg increase reported for placebo ($P < .001$). The proportion of patients with weight gain ≥ 7% did not differ statistically between treatment groups. Patients with an established diagnosis of diabetes commencing treatment with atypical antipsychotics should be monitored regularly for worsening of glucose control. For patients with risk factors for diabetes, fasting blood glucose testing is recommended when initiating treatment with an atypical antipsychotic and periodically throughout treatment. All patients should be monitored for symptoms of hyperglycemia. A similar approach has been recommended for patients with schizophrenia and other severe mental illnesses.[50–52] Close clinical monitoring of the weight and BMI of patients periodically throughout the treatment period is also essential. Physicians are also advised that blood lipid levels may be affected by atypical antipsychotics.

These findings underscore the efficacy and tolerability of quetiapine monotherapy in bipolar depression, a historically understudied indication. By demonstrating the effectiveness of quetiapine monotherapy over both placebo and paroxetine, this study provides valuable evidence to support the use of quetiapine as a first-line treatment option for the acute management of bipolar depression. The common practice of employing antidepressants (often as monotherapy) to treat bipolar I and in particular bipolar II depressed patients appears to need reexamination by clinicians in light of this study and the STEP-BD results.[16]

Drug names: aripiprazole (Abilify), bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Equetro, and others), divalproex (Depakote and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine-fluoxetine combination (Symbyax), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal and others), venlafaxine (Effexor and others), zaleplon (Sonata and others), zolpidem (Ambien, Edluar, and others), zopiclone (Lunesta).

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