Efficacy of Quetiapine Monotherapy for the Treatment of Depressive Episodes in Bipolar I Disorder: A Post Hoc Analysis of Combined Results From 2 Double-Blind, Randomized, Placebo-Controlled Studies

Richard H. Weisler, M.D.; Joseph R. Calabrese, M.D.; Michael E. Thase, M.D.; Robert Arvekvist, M.Sc.; Göran Stening, Ph.D.; Björn Paulsson, M.D.; and Trisha Suppes, M.D., Ph.D.

Objective: To investigate the efficacy and tolerability of quetiapine monotherapy for the treatment of major depressive episodes in patients with bipolar I disorder, as a post hoc analysis of data from 2 large studies, the BipOLar DEpRession (BOLDER) I and II studies, which investigated the overall efficacy of quetiapine in both bipolar I and II disorder.

Method: A combined cohort of patients with depressive episodes in bipolar I disorder (DSM-IV criteria) (N = 694) from 2 nearly identical double-blind, randomized, placebo-controlled studies that each randomly assigned patients with bipolar I and II disorder to 8 weeks of treatment with quetiapine 300 or 600 mg/day or placebo was analyzed. The primary efficacy measure was change from baseline to end of treatment (week 8) in the Montgomery-Asberg Depression Rating Scale (MADRS) total scores.

Results: In the combined cohort of patients with depressive episodes in bipolar I disorder from 2 studies, there were significantly greater clinical improvements in mean MADRS total scores among patients who received quetiapine compared with placebo from baseline to week 1 and through week 8 (at week 8: quetiapine 300 mg/day = –19.4; 600 mg/day = –19.6; placebo = –12.6; $p < .001$ for each dose), providing effect sizes of 0.78 and 0.80, respectively. Changes in MADRS were unrelated to reports of sedation and somnolence. The most common adverse events (AEs) with quetiapine were dry mouth, somnolence, sedation, dizziness, and constipation. Rates of withdrawal because of these AEs were relatively low.

Conclusions: Quetiapine monotherapy (300 and 600 mg/day) is more effective than placebo and generally well tolerated for the treatment of depressive episodes in patients with bipolar I disorder.

(J Clin Psychiatry 2008;69:769–782)

Received Aug. 17, 2007; accepted Feb. 29, 2008. *From the Department of Psychiatry and Behavioral Science, Duke University Medical Center and the Department of Psychiatry, University of North Carolina at Chapel Hill, Raleigh, N.C. (Dr. Weisler); University Hospitals Cleveland/Case University School of Medicine, Ohio (Dr. Calabrese); Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pa. (Dr. Thase); AstraZeneca Pharmaceuticals, Södertälje, Sweden (Drs. Stening and Paulsson and Mr. Arvekvist); and the Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas (Dr. Suppes).*

This study was supported by AstraZeneca Pharmaceuticals LP, Wilmington, Del. (5077US/0049 [BOLDER I] and D1447C00135 [BOLDER II]).

These results were presented in part at the 159th annual meeting of the American Psychiatric Association; May 20–25, 2006; Toronto, Ontario, Canada; the XXVth Biennial Collegium Internationale Neuro-Psychopharmacologium Congress; July 9–13, 2006; Chicago, Ill.; and the Fifth European Stanley Conference on Bipolar Disorder; Oct 5–7, 2006; Barcelona, Spain.

Financial disclosure appears at the end of the article.

A list of principal investigators in the BOLDER I and II studies was published previously (Am J Psychiatry 2005;162:1351–1360; J Clin Psychopharmacol 2006;26:600–609). The authors acknowledge the assistance of Clare Wheatcroft, Ph.D. (PAREXEL MMS), who provided medical writing assistance on behalf of AstraZeneca.

Corresponding author and reprints: Richard H. Weisler, M.D., Department of Psychiatry, University of North Carolina at Chapel Hill, 700 Spring Forest, Suite 125, Raleigh, NC 27609 (e-mail: RWeisler@aol.com).

The treatment of acute bipolar depression remains understudied, although interest in this area is increasing.[1] The limited number of randomized, controlled trials is especially notable, since depressive symptoms and episodes often dominate the course of the illness[2–4] and are associated with functional impairment,[5,6] suicide,[7–10] and other causes of increased mortality.[11] Current treatment options for the management of bipolar I depression include mood-stabilizing medications, such as lithium, and atypical antipsychotics, either alone or in combination with antidepressants.[12,13]

A small number of placebo-controlled, randomized, parallel-group clinical trials of other monotherapies in acute bipolar I depression have been reported in the past decade.[14–20] Despite preliminary evidence supporting the efficacy of the anticonvulsants, lamotrigine[14,15] and divalproex,[16,19] other acute trials have failed to show efficacy in acute bipolar depression.[21,22]

In comparison, 3 published studies of atypical antipsychotic therapy in bipolar depression have yielded evidence of significant antidepressant efficacy. One study compared olanzapine, the combination of olanzapine and fluoxetine, and placebo in an 8-week trial of 833 patients.[17] Both active treatment groups had significantly greater reductions in the Montgomery-Asberg Depression Rating Scale (MADRS)[23] total scores from baseline to end point beginning at week 1. The olanzapine and fluoxetine combination group (effect size = 0.68; N = 82) displayed significantly greater improvement over olanzapine monotherapy (effect size = 0.32; N = 351) from week 4 through week 8. In a more recent study, the olanzapine and fluoxetine combination was compared with lamotrigine in a 7-week trial of patients with bipolar I depression.[24] The results showed that patients treated with the olanzapine and fluoxetine combination had significantly greater reductions in both depressive and manic symptoms as assessed on the Clinical Global Impressions-Severity of Illness scale (CGI-S), the MADRS, and the Young Mania Rating Scale (YMRS)[25] than those treated with lamotrigine.

The study also indicated that treatment with the olanzapine and fluoxetine combination resulted in more treatment-emergent adverse events (AEs), greater weight gain, and significantly elevated levels of total cholesterol and triglycerides compared with lamotrigine. Two recent studies have, however, found that the atypical antipsychotic aripiprazole did not provide a better risk-to-benefit ratio over placebo for the treatment of patients with bipolar I disorder experiencing a major depressive episode; there were significant differences in favor of aripiprazole in the early weeks of the study but not at end point.[26] The results from studies and evidence of improvement in depressive symptoms in clinical trials of quetiapine in patients with schizophrenia and schizoaffective disorder[27,28] suggested that quetiapine might also exert acute antidepressant effects in patients with bipolar I depression.

The results reported here are from a cohort of patients with depressed episodes in bipolar I disorder from two 8-week, multicenter, randomized, placebo-controlled studies (BipOLar DEpRession [BOLDER] I and II). These 2 studies were conducted to evaluate the efficacy and tolerability of quetiapine monotherapy versus placebo in the treatment of a major depressive episode in adult patients with bipolar I or II disorder.[18,20] These data represent a more detailed analysis of major depressed episodes specifically in the subpopulation of patients with bipolar I disorder than has been undertaken previously. Data from both quetiapine studies separately and a combined analysis of patients from both studies are presented in order to be able to compare the efficacy and safety results with those from other published studies that included only patients with bipolar I disorder.[14,17] This approach will allow comparisons on multiple domains of efficacy and safety for any possible future meta-analyses particularly for patients with bipolar I or II disorder separately. In addition, this combined analysis provides a larger, more generalizable data set to inform clinicians when making treatment decisions for these patients and provides detailed analyses of patients with bipolar I disorder that were not included in the original individual studies of patients with bipolar I and II disorder.[18,20]

METHOD

Study Design

Two multicenter, randomized, double-blind, placebo-controlled, parallel-group trials were conducted to compare fixed doses of quetiapine (300 and 600 mg/day) with placebo for the treatment of a major depressive episode among patients with either bipolar I or II disorder.[18,20] Data presented here are from a separate post hoc analysis of a cohort of patients with major depressed episodes in bipolar I disorder (approximately two thirds of the patients in the original studies). A separate similar post hoc analysis of a cohort of patients with major depressed episodes in bipolar II disorder has been reported.[29] The studies were performed in accordance with the current amendment of the Declaration of Helsinki and International Conference on Harmonization/Good Clinical Practice guidelines. Patients provided written, informed consent prior to screening after a complete explanation of the study procedures. The study protocols and all subsequent amendments were approved by the appropriate institutional review boards.

In both studies, an initial washout period of 7 to 28 days (depending on the medications involved) served to taper and eliminate ongoing antidepressants, antipsychotics, and any mood-stabilizing medications. Following washout, patients were randomly assigned (1:1:1) for 8 weeks to one of 3 treatment groups: quetiapine 300 mg/day, quetiapine 600 mg/day, or placebo.

Quetiapine was administered in a blinded manner, and the dose was gradually increased over 4 days to a total daily dose of 300 mg/day by day 4 of the study or to a total daily dose of 600 mg/day by the end of week 1. Fixed-dose treatment was continued up to 8 weeks. One-time dose reductions of 100 mg/day (i.e., to 200 mg/day and 500 mg/day) were permitted in all active treatment groups for intolerability after week 1, at the discretion of the investigator. Quetiapine and placebo were administered once daily at bedtime in accordance with the regular dosing schedule for medications used to treat depression. All packaging of treatments was identical, with placebo and active tablets identical in size and color. Adherence to treatment was assessed by returned tablet counts.

Patients were permitted to continue using medications for medical and nonpsychiatric illnesses, as well as for oral contraception. During the first 3 weeks of the study,

zolpidem (5–10 mg/day) at bedtime for insomnia and/or lorazepam (1–3 mg/day) for severe anxiety was also permitted.

Patient Population

In both studies, outpatients, aged 18 to 65 years, with a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[30] diagnosis of bipolar I or II disorder were eligible. For inclusion in either study, patients were required to be currently experiencing a major depressive episode by DSM-IV criteria (duration < 1 year and > 4 weeks from screening). Patients were also required to have a 17-item Hamilton Rating Scale for Depression (HAM-D)[31] total score of ≥ 20 points, a score of ≥ 2 points on HAM-D item 1 (depressed mood), and a score of ≤ 12 points on the YMRS. Inclusion criteria were based on the HAM-D scale rather than the primary efficacy measure (MADRS). Patients with a rapid-cycling disease course, defined as the occurrence of at least 4 prior mood episodes during the previous 12 months, were also included. In BOLDER II, however, patients could not have experienced more than 8 mood events in the previous year. Female patients of child-bearing potential were required to have a negative pregnancy test and to use adequate contraception for the duration of the study. The exclusion criteria were similar in both studies and have been described in detail elsewhere.[18,20] Briefly, patients with a current diagnosis of an Axis I disorder (other than bipolar disorder) that had been the primary focus of treatment within 6 months of screening, those with a history of nonresponse to more than 2 adequate trials of antidepressants, and those with clinically significant medical illnesses or who posed a current serious suicide or homicide risk were excluded. This report is a post hoc analysis of those patients with bipolar I disorder combined from the 2 studies. Primary outcome measure in the 2 individual BOLDER studies for patients with bipolar I disorder and the overall combined BOLDER I and II results in patients with bipolar I and II disorder are also included.

Efficacy Evaluations

The primary efficacy measure in both studies and this post hoc analysis of patients with major depressive episodes in bipolar I disorder was change from baseline at week 8 in MADRS total scores. Secondary efficacy variables were the proportion of patients who achieved a response to treatment (defined as a ≥ 50% decrease in MADRS total scores from baseline); the proportion of patients who achieved remission (defined as a reduction in MADRS score to ≤ 12); the change from baseline in MADRS individual items, HAM-D total scores, HAM-D item 1 (depressed mood) score, HAM-D item 3 (suicide) score, Hamilton Rating Scale for Anxiety (HAM-A)[32] total scores, and CGI-S score; and the proportion of patients rated as "much improved" or "very much improved" on the Clinical Global Impressions-Improvement scale (CGI-I).[33] Health-related quality of life was assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire short form (Q-LES-Q SF),[34] which includes 16 items to assess social relationships, living/housing, physical health and medication, and global satisfaction. In the BOLDER I study only, quality of sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI),[35] while in BOLDER II only, the Sheehan Disability Scale (SDS)[36] was used to assess functional impairment. In addition, an analysis to determine if there were any predictors of response to treatment was conducted by determining the MADRS response rates according to various baseline demographic and disease characteristics.

Most clinical assessments were conducted at baseline and weekly from week 1 (i.e., 7 days after the start of treatment) through week 8. The CGI-I was assessed from week 1 onward in both studies; the HAM-A was assessed weekly in the BOLDER I study and at baseline and weeks 1, 4, and 8 in the BOLDER II study; and the Q-LES-Q analysis was conducted at baseline and at weeks 4 and 8 in both studies. The PSQI in BOLDER I and the SDS in BOLDER II were conducted at weeks 4 and 8.

Safety and Tolerability Evaluations

In both studies, safety and tolerability were assessed each week by recording spontaneously reported AEs and reasons for withdrawal from the trial, including those due to AEs. All AEs chosen by the investigator were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) classification system. Extrapyramidal symptoms (EPS), which included AEs of akathisia, dyskinesia, dystonia, extrapyramidal disorder, muscle contractions, involuntary muscle rigidity, psychomotor hyperactivity, restlessness, or tremor, were also evaluated using the Simpson-Angus Scale (SAS)[37] and the Barnes Akathisia Rating Scale (BARS).[38] In addition, all patients completed the YMRS each week to assess the emergence of manic symptoms. Patients having a YMRS total score ≥ 16 on 2 consecutive assessments or an adverse event of mania or hypomania were considered to have experienced treatment-emergent mania. Vital signs and weight were recorded, and 12-lead electrocardiograms and routine hematology and laboratory tests were also conducted.

Statistical Analyses

This report presents a post hoc analysis of individual and combined data from 2 large studies of depressed patients with bipolar I and II disorder.

Efficacy analyses were performed using the intent-to-treat (ITT) population (those who received at least 1 dose of study medication and had at least 1 postbaseline

efficacy assessment) and using mixed-model repeated-measures (MMRM) methodology, with baseline value as covariate; treatment, visit, and treatment-visit interaction as fixed effects; and center as random effect and repeated over time. Effect sizes (improvement of quetiapine over placebo divided by pooled SD) were calculated using estimates from the MMRM analysis.[39]

Cochran-Mantel-Haenszel χ^2 tests were used to assess dichotomous variables, such as MADRS response and remission rates at each assessment, and the proportion of patients achieving improvement on the CGI-I in the 2 quetiapine treatment groups compared with placebo. The median time to first response and remission was calculated using the Kaplan-Meier method.

The change from baseline in each assessment score (i.e., HAM-D, HAM-A, CGI-S, YMRS, and Q-LES-Q) was analyzed using MMRM.

Descriptive statistics were used for safety variables, including AEs. These presentations are based on data from all patients who received at least 1 dose of the study medication (safety population).

All analyses were performed using SAS statistical software version 8.02 (SAS Institute Inc., Cary, N.C.). A p value of less than .05 was considered statistically significant. No adjustment for multiple comparisons for the secondary analyses was conducted.

RESULTS

In total, a cohort of 694 patients with depressed episodes of bipolar I disorder combined from 2 studies was randomly allocated to receive quetiapine 300 mg/day (N = 232), quetiapine 600 mg/day (N = 232), or placebo (N = 230) for 8 weeks; these subjects were included in the safety population, as they had at least 1 dose of treatment. There were no differences in the illness history between the groups, with a mean (SD) number of prior depressed episodes of 13.5 (14.8) in the quetiapine 300-mg/day group, 16.6 (18.8) in the quetiapine 600-mg/day group, and 16.6 (24.4) in the placebo group. The proportion of patients who completed the 2 studies was 64.2% in the quetiapine 300-mg/day group, 55.2% in the quetiapine 600-mg/day group, and 60.0% in the placebo group. The reasons for discontinuation are shown in Figure 1. The ITT population (N = 657), which included all patients who received 1 dose of treatment and had at least 1 post-baseline efficacy assessment, consisted of 220 patients in the quetiapine 300-mg/day group, 215 patients in the quetiapine 600-mg/day group, and 222 patients in the placebo group.

The 3 treatment groups had similar baseline demographic and illness characteristics (Tables 1 and 2). All patients with bipolar I disorder treated in the 2 studies had moderate to severe depression, with mean baseline MADRS scores of 31.1 for quetiapine 300 mg/day, 30.3 for quetiapine 600 mg/day, and 30.8 for placebo (Table 2). The baseline YMRS scores were also similar among those treated with quetiapine 300 mg/day, quetiapine 600 mg/day, and placebo (mean 5.6, 5.4, and 5.4, respectively).

There was a similar use of the permitted concomitant medications for the first 3 weeks of the study across the quetiapine-treated groups, with slightly higher rates in the placebo group. Patients could use both zolpidem and lorazepam. Zolpidem was used by 2.6% of the patients in the quetiapine 300-mg/day group, 4.7% in the quetiapine 600-mg/day group, and 7.4% in the placebo group, and lorazepam was used by 4.7%, 5.6%, and 8.3%, respectively.

It should be noted that 19.8% of patients receiving quetiapine 300 mg/day and 24.1% of patients receiving quetiapine 600 mg/day in the combined studies had their dosage adjusted downward by 100 mg/day for intolerability reasons compared with 4.3% of patients receiving placebo.

Depressive Symptoms

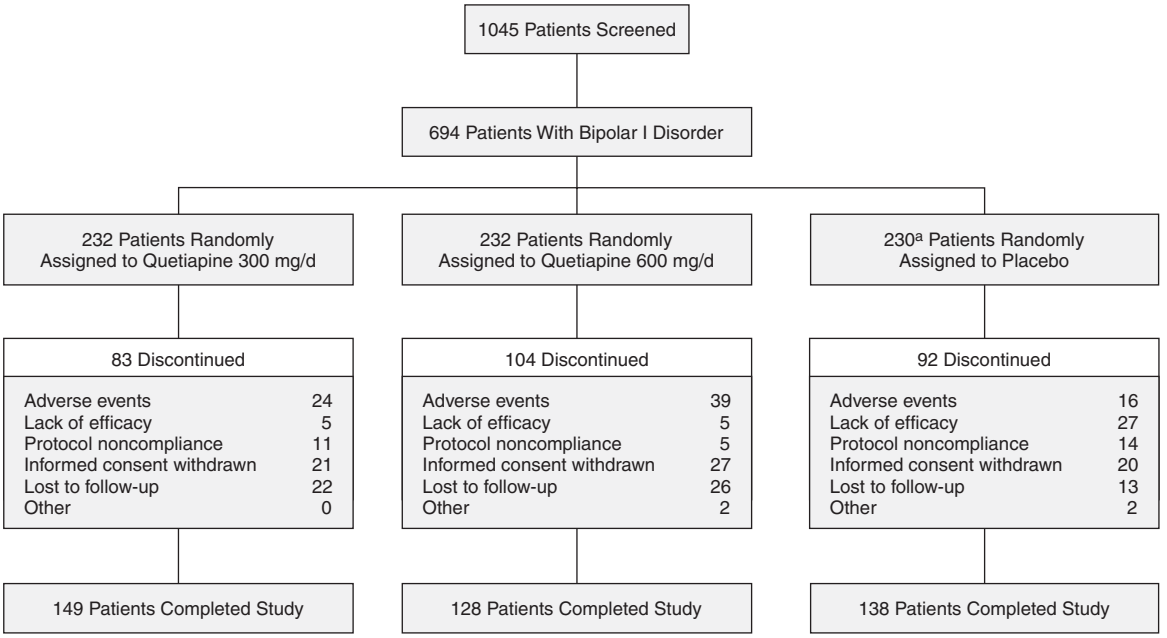
Montgomery-Asberg Depression Rating Scale.

MADRS change from baseline. In the combined analysis, depressed patients with bipolar I disorder in the quetiapine 300- and 600-mg/day treatment groups showed statistically significant improvements in symptoms of depression compared with those in the placebo group throughout the 8-week treatment period ($p < .001$), starting with the first evaluation (week 1) and sustained to study end (week 8). At week 8, the mean change from baseline in MADRS total scores was –19.4 in the quetiapine 300-mg/day group and –19.6 in the quetiapine 600-mg/day group compared with –12.6 in the placebo group ($p < .001$ for each quetiapine dose vs. placebo; Figure 2A), with large effect sizes of 0.78 and 0.80, respectively. These results are similar to those observed in the overall combined data from BOLDER I and II in patients with bipolar I and II disorder (Figure 2B). There were also similar results seen in the 2 individual BOLDER I and II studies in the patients with bipolar I disorder (Figures 2C and D).

Because the study designs, baseline patient characteristics, and efficacy on MADRS total scores (Figure 2) were similar in the 2 studies, all subsequent analyses have been conducted on the combined bipolar I patient cohort.

In patients with bipolar I disorder and a rapid-cycling disease course, there were significant improvements over placebo for both doses of quetiapine, with mean change from baseline on MADRS at week 8 of –20.3 for quetiapine 300 mg/day (N = 58) and –20.2 for quetiapine 600 mg/day (N = 50) versus –13.1 for placebo (N = 61) ($p < .001$ for each dose vs. placebo). For bipolar I patients without a rapid-cycling disease course, there were also significant improvements compared with placebo (–19.2 for quetiapine 300 mg/day [N = 162] and –19.3 for quetiapine 600 mg/day [N = 165] vs. –12.4 for placebo [N = 161]; $p < .001$ for each dose vs. placebo).

Figure 1. Disposition of Study Population



[a]One patient in the placebo group did not receive treatment. The intent-to-treat population consisted of 220 patients in the quetiapine 300-mg/day group, 215 patients in the quetiapine 600-mg/day group, and 222 patients in the placebo group.

Table 1. Demographic and Illness Characteristics at Baseline of Patients With Bipolar I Disorder (combined ITT population)

Characteristic	Quetiapine 300 mg/d (N = 220)	Quetiapine 600 mg/d (N = 215)	Placebo (N = 222)
Sex, %			
Male	47.7	41.9	41.9
Female	52.3	58.1	58.1
Age, mean (SD), y	36.9 (10.9)	38.2 (11.5)	38.6 (11.2)
Weight, mean (SD), kg	87.2 (21.5)	87.1 (23.3)	84.3 (23.0)
Bipolar disorder, %			
Rapid cyclers	26.4	23.3	27.5
Nonrapid cyclers	73.6	76.7	72.5

Abbreviation: ITT = intent-to-treat.

MADRS items analysis. The core mood symptoms of depression and all other MADRS items significantly improved from baseline in the quetiapine 300- and 600-mg/day dose groups compared with placebo at week 8 (all p values < .001, except reduced appetite p < .05; Figure 3). Already at week one, 6 MADRS item scores (apparent sadness, reported sadness, inner tension, reduced sleep, inability to feel, and suicidal thoughts) significantly improved from baseline for each quetiapine dose compared with placebo (p < .05). Two additional MADRS items (concentration difficulties and pessimistic thoughts) reached statistical significance for both quetiapine doses compared with placebo at week 2.

Response rate. Within the first week, significantly more patients treated with quetiapine 600 mg/day had responded (≥ 50% decrease in MADRS total scores from baseline) compared with placebo (24.1% vs. 12.2%, p = .001; Figure 4A). The response in patients treated with quetiapine 300 mg/day was 17.5% (p = .115 vs. placebo). By week 2, both quetiapine groups had a significantly greater proportion of responders than placebo (39.5% and 36.6% vs. 19.8%; p < .001 for each dose). At week 8, significantly more patients had responded to quetiapine 300 mg/day (60.9%) or quetiapine 600 mg/day (61.4%) compared with placebo (38.7%) (p < .001 for each dose vs. placebo; Figure 4A). The median time to first response was 22 days in both quetiapine (300 and 600 mg/day) groups versus 36 days in the placebo group (p < .001 for each dose vs. placebo).

Predictors of response. The MADRS response rates were examined according to various baseline demographic and disease characteristics. The results indicate that both doses of quetiapine demonstrate higher response rates than placebo for the following parameters: (1) all racial/ethnic categories, (2) both sexes, (3) those with and without a history of rapid cycling, (4) those with and without prior medication use prior to the start of the study (including the use of antidepressants, antipsychotics, and bipolar medications separately), (5) those with and without baseline MADRS total scores ≥ 26, (6) those with and without baseline YMRS total scores ≥ 6, (7) those with

Table 2. Baseline and Mean Change in Efficacy Measures at Week 1 and Week 8 in Outpatients With Bipolar I Depression (combined ITT, MMRM)[a]

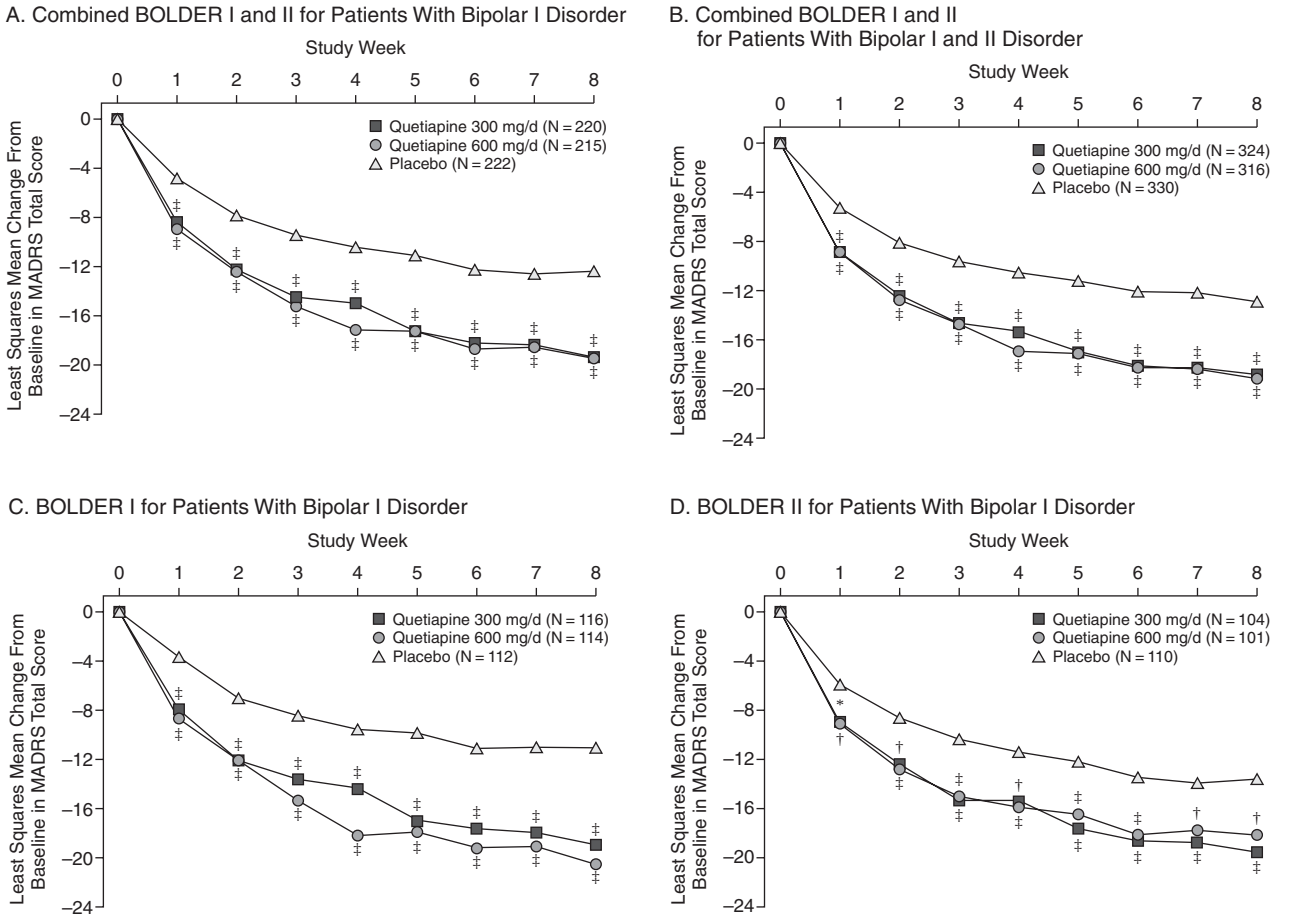
Measure and Treatment	Baseline Score Mean	Baseline Score SD	Change in Score at Week 1	Week 1 Analysis[b] MMRM	Week 1 Analysis[b] p Value	Change in Score at Week 8	Week 8 Analysis[b] MMRM	Week 8 Analysis[b] p Value
MADRS								
Quetiapine 300 mg/d	31.1	5.18	–8.6	–3.5	< .001	–19.4	–6.8	< .001
Quetiapine 600 mg/d	30.3	5.66	–9.1	–4.0	< .001	–19.6	–7.0	< .001
Placebo	30.8	5.26	–5.0	…	…	–12.6	…	…
HAM-D total								
Quetiapine 300 mg/d	24.9	3.37	–7.6	–2.9	< .001	–15.3	–5.3	< .001
Quetiapine 600 mg/d	24.8	3.41	–7.7	–3.0	< .001	–15.6	–5.6	< .001
Placebo	24.5	3.32	–4.6	…	…	–10.0	…	…
HAM-D item 1 (depressed mood)								
Quetiapine 300 mg/d	2.9	0.5	–0.7	–0.3	.005	–2.0	–0.6	< .001
Quetiapine 600 mg/d	2.9	0.5	–0.7	–0.3	.001	–1.9	–0.6	< .001
Placebo	3.0	0.5	–0.4	…	…	–1.4	…	…
HAM-D item 3 (suicide)								
Quetiapine 300 mg/d	0.9	0.8	–0.4	–0.2	.005	–0.7	–0.2	< .001
Quetiapine 600 mg/d	0.9	0.8	–0.3	–0.1	.093	–0.7	–0.2	.002
Placebo	0.8	0.8	–0.2	…	…	–0.5	…	…
CGI-I[c]								
Quetiapine 300 mg/d	…	…	3.2	–0.4	< .001	1.9	–0.9	< .001
Quetiapine 600 mg/d	…	…	3.2	–0.5	< .001	2.0	–0.8	< .001
Placebo	…	…	3.6	…	…	2.8	…	…
CGI-S								
Quetiapine 300 mg/d	4.5	0.59	–0.5	–0.3	.002	–2.0	–0.8	< .001
Quetiapine 600 mg/d	4.6	0.60	–0.5	–0.3	.002	–2.0	–0.9	< .001
Placebo	4.5	0.59	–0.2	…	…	–1.1	…	…
HAM-A								
Quetiapine 300 mg/d	18.5	6.95	–4.3	–1.7	.002	–10.1	–4.2	< .001
Quetiapine 600 mg/d	18.5	6.99	–4.3	–1.7	.003	–10.5	–4.5	< .001
Placebo	18.2	6.82	–2.6	…	…	–6.0	…	…
Q-LES-Q SF								
Quetiapine 300 mg/d	35.4	8.5	…	…	…	11.0	4.2	< .001
Quetiapine 600 mg/d	35.6	8.2	…	…	…	12.3	5.5	< .001
Placebo	35.7	7.4	…	…	…	6.8	…	…

[a]Quetiapine 300 mg/day, N = 220; quetiapine 600 mg/day, N = 215; and placebo, N = 222.
[b]Comparison with placebo.
[c]Values are actual scores rather than change in scores.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, ITT = intent-to-treat, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed-model repeated measures, Q-LES-Q SF = Quality of Life Enjoyment and Satisfaction Questionnaire short form.
Symbol: … = not applicable.

and without baseline HAM-A total scores ≥ 19, and (8) those experiencing or not experiencing sedative effects at any time during treatment. There were no differential effects in body mass index or weight between MADRS responders (≥ 50% decrease in MADRS total scores) and nonresponders. After adjusting for placebo response by calculating the difference between the rates for the combined quetiapine groups and placebo group, there were slightly higher responses found in men versus women (25.5% vs. 20.2%, respectively), in those with a history of rapid cycling versus no history of rapid cycling (28.3% vs. 20.5%, respectively), in those with baseline MADRS total scores < 26 versus those with a score ≥ 26 (29.8% vs. 21.0%, respectively), and in those without sedative effects reported versus those with sedative effects (23.5% vs. 9.1%, respectively). There were similar outcomes noted in all racial/ethnic categories, in those with and without medication (antidepressants, antipsychotics, and other bipolar medications) use prior to the start of the study, in those with and without baseline YMRS scores ≥ 6, and in those with and without baseline HAM-A total scores ≥ 19 after adjusting for placebo response.

Remission. Remission (MADRS total scores ≤ 12) at end of treatment (week 8) was achieved in 53.6% ($p < .001$) of patients treated with quetiapine 300 mg/day, 55.3% ($p < .001$) treated with quetiapine 600 mg/day, and 31.5% of those receiving placebo (Figure 4B). Within the first week of treatment, remission was achieved in significantly more patients treated with quetiapine 600 mg/day (16.5%, $p = .008$) than those treated with placebo (8.1%). The proportion of patients treated with quetiapine 300 mg/day who achieved remission doubled from week 1 to week 2 (from 12.4% to 25.5%) and was significantly different from placebo by week 2 ($p = .002$). The median time to remission was 28 days in both quetiapine groups compared with 44 days in the placebo group ($p < .001$ for each dose vs. placebo).

Figure 2. Mean Change From Baseline in MADRS Total Scores at Each Assessment Among Patients With Bipolar I Disorder (ITT, MMRM)



*p < .05 vs. placebo.
†p < .01 vs. placebo.
‡p < .001 vs. placebo.
Abbreviations: BOLDER = BipOLar DEpRession study, ITT = intent-to-treat, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed-model repeated measures.

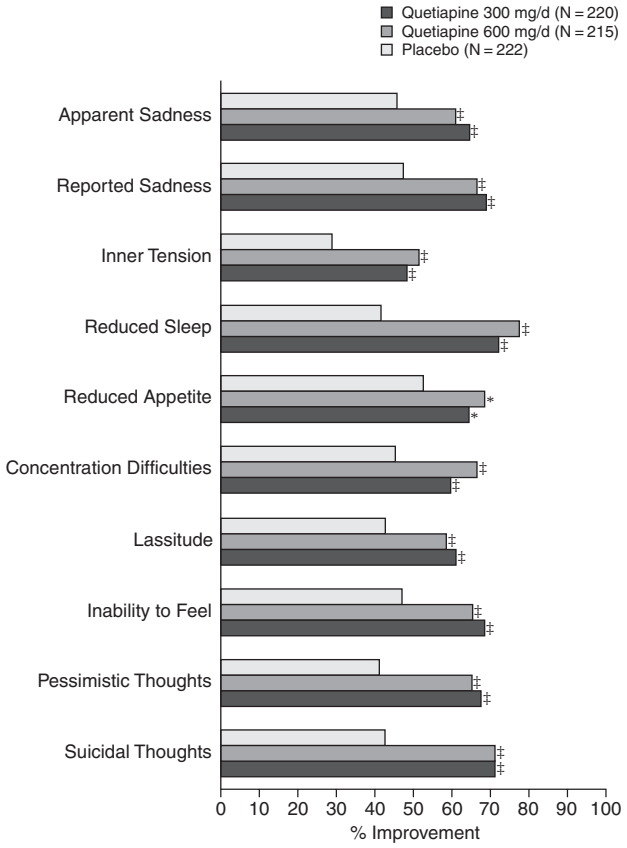
Potential impact of sedation/somnolence. In order to evaluate the contribution, if any, of sedative side effects to the efficacy of quetiapine in improving depressive symptoms in these patients, a further analysis was performed on patients who did and did not experience AEs of sedation, somnolence, lethargy, or sluggishness at any time during the studies. The MADRS total score change from baseline at week 8 was similar in both quetiapine dose groups in those with and without somnolence and/or sedation and greater in both cases than placebo (patients with somnolence/sedation –17.2 for quetiapine 300 mg/day [N = 137] and –17.5 for quetiapine 600 mg/day [N = 139] vs. –16.1 for placebo [N = 36]; and patients without somnolence/sedation –17.5 for quetiapine 300 mg/day [N = 83] and –16.6 for quetiapine 600 mg/day [N = 76] vs. –9.7 for placebo [N = 186]). The weekly change in MADRS total scores (descriptive statistics) in patients with and without somnolence and/or sedation is shown in Figure 5.

Hamilton Rating Scale for Depression. As in MADRS total scores, quetiapine (300 or 600 mg/day) was significantly more effective than placebo at reducing HAM-D total scores as early as week 1 ($p < .001$) and up to study end point, week 8 ($p < .001$; Figure 6 and Table 2). There were also greater mean reductions from baseline to week 1 and through study end (week 8) in HAM-D item 1 (depressed mood) and item 3 (suicide) score in patients treated with quetiapine 300 mg/day or 600 mg/day compared with placebo (Table 2).

Illness Severity and Overall Improvement

The severity of illness as assessed by change from baseline to end of treatment in CGI-S score was significantly reduced at week 1 in patients treated with

Figure 3. Percentage Improvement From Baseline to Week 8 in Individual MADRS Items Among Patients With Bipolar I Disorder (combined ITT, MMRM)[a]



[a]p Values based on change-from-baseline MMRM analyses.
*p < .05 vs. placebo.
‡p < .001 vs. placebo.
Abbreviations: ITT = intent-to-treat, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed-model repeated measures.

quetiapine 300 or 600 mg/day compared with those who received placebo ($p < .01$ for each dose) and was sustained to study end (week 8; $p < .001$; Table 2).

At the final assessment, the proportion of patients rated as "much improved" or "very much improved" on the CGI-I was 65.5% for the quetiapine 300-mg/day group, 60.9% for the quetiapine 600-mg/day group, and 34.2% for the placebo group ($p < .001$ for each dose). By week 1 of treatment, 18.0% and 23.1% of patients treated with quetiapine 300 and 600 mg/day, respectively, were rated on the CGI-I as "much improved" or "very much improved" compared with 10.8% of patients treated with placebo ($p < .05$ for 300 mg/day and $p < .001$ for 600 mg/day).

Anxiety Symptoms

Quetiapine at either dose in this combined analysis was significantly more effective than placebo at reducing anxiety symptoms from week 1 ($p < .01$) to study end (week 8; $p < .001$; Table 2).

Quality of Life

Quetiapine treatment (both doses) significantly improved quality of life from baseline to end of treatment as measured by the Q-LES-Q SF ($p < .001$; Table 2).

Quality of Sleep

In the BOLDER I study only, the PSQI was used to assess the improvement in patients' quality of sleep. In BOLDER I, there were significant improvements in the quality of sleep, with the mean change from baseline to week 8 of –5.5 for quetiapine 300 mg/day (N = 81) and –5.9 for quetiapine 600 mg/day (N = 67) vs. –2.9 for placebo (N = 62) ($p < .001$ for each dose vs. placebo) for patients with bipolar I disorder.

Overall Functioning

In the BOLDER II study only, the severity of impairment in functioning caused by symptoms was assessed using the SDS. In the patients with bipolar I disorder in BOLDER II, both quetiapine treatment groups were associated with numerical but not statistically significant improvements over those treated with placebo in level of impairment (mean change from baseline to week 8 on SDS: –7.7 for quetiapine 300 mg/day [N = 63] and –6.9 for quetiapine 600 mg/day [N = 65] vs. –6.0 for placebo [N = 78]).

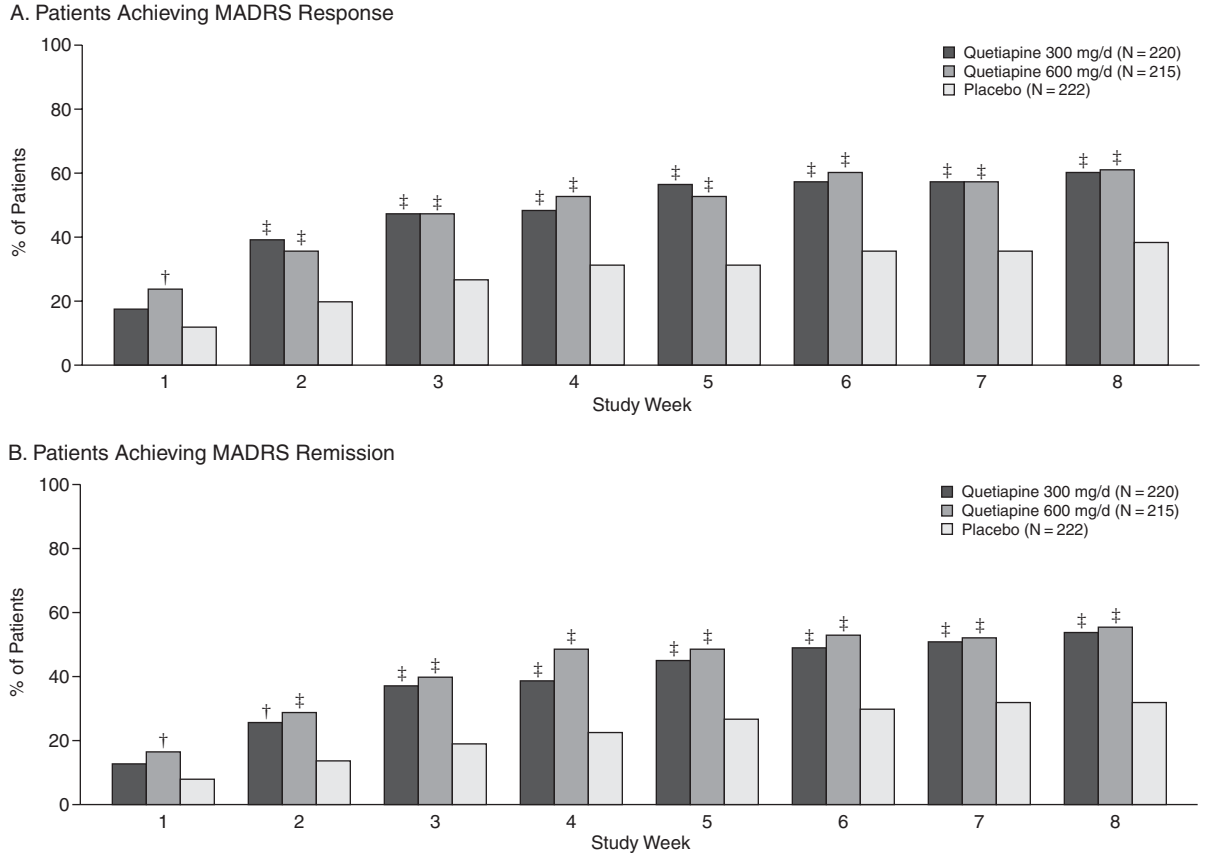
Safety and Tolerability

No deaths occurred during either of the studies. The most common reason for withdrawal from treatment in both quetiapine groups was AEs (10.3% quetiapine 300 mg/day, 16.8% quetiapine 600 mg/day, 7.0% placebo), and the most common reason for withdrawal in the placebo group was lack of efficacy (11.7% in placebo vs. 2.2% in both quetiapine groups; Figure 1). Fewer patients from the quetiapine 300-mg/day group withdrew because of an adverse event than from the quetiapine 600-mg/day group. AEs that most frequently led to study discontinuation included sedation or somnolence and, to a lesser extent, nausea and dizziness.

Adverse events. AEs (whether or not related to study drug) occurring in ≥ 10% of patients in any of the 2 quetiapine groups and at twice the rate of placebo are shown in Table 3. The most common AEs were dry mouth, somnolence, sedation, dizziness, and constipation.

Approximately one third of patients in each quetiapine group experienced somnolence, and up to one quarter of patients in each quetiapine group experienced sedation, as reported using MedDRA terms. Approximately 5% to 7% of patients withdrew from active treatment because of either somnolence or sedation (quetiapine 300 mg/day, 6.9%; quetiapine 600 mg/day, 5.6%; placebo, 0%). Most

Figure 4. Proportion of Patients With Bipolar I Disorder Who Achieved (A) a Response to Treatment (≥50% decrease in mean MADRS scores from baseline) and (B) Remission (reduction in MADRS scores to ≤12) at Each Assessment (combined ITT, LOCF)



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

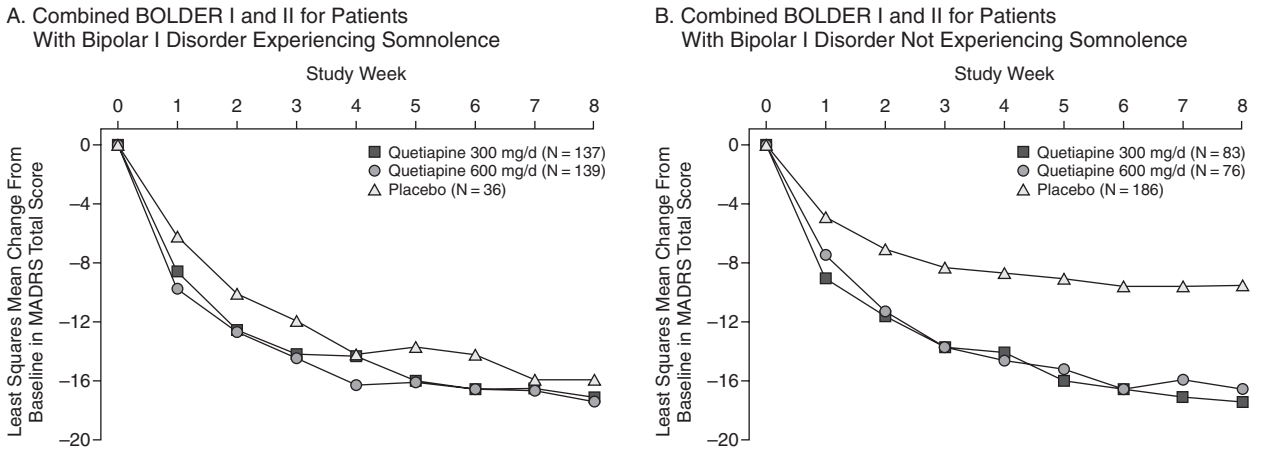
of these discontinuations occurred in the first week of treatment.

EPS-related adverse events. The incidence of AEs related to EPS was 11.2% in the quetiapine 300-mg/day group and 11.6% in the quetiapine 600-mg/day group compared with 3.9% in the placebo group. Overall, these AEs led to discontinuations in 0.4% and 1.7% of the quetiapine 300- and 600-mg/day groups, respectively, versus 0.4% in the placebo group. The most frequently reported AEs related to EPS were extrapyramidal disorder (3.4% in both quetiapine groups vs. 1.3% in placebo group), akathisia (3.0% in both quetiapine groups vs. 0.4% in placebo), and tremor (1.7% in quetiapine 300-mg/day group, 2.6% in quetiapine 600-mg/day group vs. 0.9% in placebo group).

Mean baseline SAS scores were 0.4 in the quetiapine 300-mg/day group, 0.6 in the quetiapine 600-mg/day group, and 0.4 in the placebo group. Mean SAS scores worsened for 10.4% of patients in the quetiapine 300-mg/day group, 13.4% in the quetiapine 600-mg/day group, and 5.6% in the placebo group. However, there was no clinically relevant change from baseline in mean SAS total scores at week 8 (–0.2 and –0.1 vs. –0.2, respectively). Minimal changes from mean baseline scores (baseline scores 0.2, 0.3, and 0.2, respectively) were also noted in BARS scores at week 8 (–0.1 for all treatment groups), with 7.0%, 8.4%, and 7.6% of the patients showing worsening, respectively.

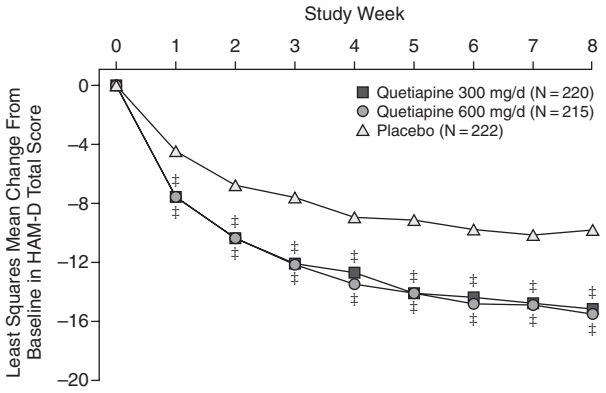
Weight gain. The mean gain in weight (change from baseline, last observation carried forward [LOCF]) was moderate in the combined patients with bipolar I disorder treated with quetiapine 300 mg/day (+0.9 kg), 600 mg/day (+1.8 kg), and placebo (+0.2 kg). In observed cases at the end of treatment, the mean corresponding gains were +0.9 kg (N = 148), +2.1 kg (N = 127), and +0.4 kg (N = 135), respectively. For those patients analyzed, the number with an increase in weight ≥ 7% from baseline was (5.4%) 10 of 186 patients treated with quetiapine

Figure 5. Mean Change From Baseline in MADRS Total Scores Among Patients With Bipolar I Disorder (A) Experiencing or (B) Not Experiencing Somnolence[a] (combined ITT, LOCF)



[a]Somnolence relates to adverse events using MedDRA terms of somnolence, sedation, lethargy, or sluggishness occurring at any time during treatment.
Abbreviations: BOLDER = BipOLar DEpRession study, ITT = intent-to-treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, MedDRA = Medical Dictionary for Regulatory Activities.

Figure 6. Mean Change From Baseline in HAM-D Total Scores Among Patients With Bipolar I Disorder (combined ITT, MMRM)



‡p < .001 vs. placebo.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, ITT = intent-to-treat, MMRM = mixed-model repeated measures.

300 mg/day, 17 (9.2%) of 184 patients treated with quetiapine 600 mg/day, and 6 (3.0%) of 199 patients treated with placebo.

Treatment-emergent mania. The incidence of treatment-emergent mania was 3.4%, 3.0%, and 6.5% in patients treated with quetiapine 300 mg/day, quetiapine 600 mg/day, and placebo, respectively. By study end (week 8), minimal changes were noted in mean change from baseline in YMRS total scores: –1.6 in patients treated with quetiapine 300 mg/day, –1.3 in those treated with quetiapine 600 mg/day, and 0 in patients who received placebo.

DISCUSSION

The results of this combined analysis of quetiapine treatment of bipolar I depression demonstrate that both the 300- and 600-mg/day doses were effective and generally well tolerated as monotherapy. Importantly, patients receiving quetiapine were somewhat less likely to experience treatment-emergent affective switches than those receiving placebo. The results of this analysis can also be compared with an analysis of the combined cohort of patients with bipolar II disorder from the 2 BOLDER studies,[29] particularly with regard to trends and differences in the overall treatment responses and tolerability in the 2 patient populations. Overall, the findings in this analysis parallel those in the patients with bipolar II depression.[29]

Although antipsychotics have previously been recommended only for incorporation into combination regimens,[12,40] growing evidence attests to their antidepressant efficacy as monotherapy, as acknowledged in practice guidelines.[13,40,41] A combination regimen of olanzapine and fluoxetine has received United States Food and Drug Administration (FDA) approval for the treatment of bipolar I depression based on a pooled analysis of 2 randomized, double-blind, 8-week studies of olanzapine monotherapy or olanzapine plus fluoxetine by Tohen et al.[17] The effect size with olanzapine monotherapy was small in the Tohen study. Quetiapine is the first agent to be approved as monotherapy for the acute treatment of depressive episodes in bipolar disorder by the FDA.[42]

Table 3. Most Commonly Reported Adverse Events (≥ 10% and twice the rate of placebo) (safety population)[a]

Adverse Event, N (%)	Quetiapine 300 mg/d (N = 232)	Quetiapine 600 mg/d (N = 232)	Placebo (N = 230)
Dry mouth	95 (40.9)	102 (44.0)	28 (12.2)
Somnolence	76 (32.8)	72 (31.0)	16 (7.0)
Sedation	60 (25.9)	62 (26.7)	19 (8.3)
Dizziness	36 (15.5)	46 (19.8)	17 (7.4)
Constipation	21 (9.1)	28 (12.1)	7 (3.0)

[a]All adverse events were coded according to the Medical Dictionary for Regulatory Activities classification system.

Quetiapine 300 mg/day is the recommended effective dose because of the equivalent efficacy and similar side effect profile in patients with bipolar depression versus the 600 mg dose of quetiapine.

In the present analysis, the onset of efficacy occurred by week 1 (first assessment), with continued improvement throughout the 8-week treatment period. Differences between quetiapine- and placebo-treated patients were statistically significant from week 1 on the primary efficacy measure (change from baseline in MADRS total scores) and on most of the secondary efficacy measures.

The antidepressant effect of quetiapine, observed as an improvement in MADRS total scores, was also supported by early and sustained improvements in the individual items of the MADRS, notably the core depressive mood symptoms (e.g., apparent and reported sadness, inability to feel, and pessimistic thoughts). The efficacy of quetiapine in the treatment of depressive symptoms was also confirmed by the significant improvements noted on the HAM-D from week 1 to end of treatment.

The suicidal thoughts item of the MADRS and the suicide item of the HAM-D were significantly improved following treatment with either quetiapine 300 or 600 mg/day compared with placebo at the initial post-randomization visit and all subsequent study visits, an important finding, given the burden of suicide risk among patients with bipolar disorder. Studies have shown that patients with bipolar disorder, and particularly those experiencing depressive episodes, are more likely to attempt and complete suicide.[43–48] Based on recent findings, the FDA has recommended a class warning for all antidepressants that any patient receiving these medications should be carefully monitored to assess any worsening of depression or increase in suicidal thinking or behavior, especially when the medications are initiated or when dosages are adjusted. In addition, the FDA has issued a health care provider alert for the use of the antiepileptic class of agents, as these have been shown to increase the risk of suicidal thoughts and behaviors in some patients.[49] The FDA advice for antiepileptics is also to carefully monitor to assess any worsening of depression or suicidality.

Effect sizes are used to estimate the magnitude of the clinical effect of treatment. A large effect size (> 0.8) would imply that fewer patients would need to be treated to see the effect of the drug. Although comparisons of effect sizes between different studies are potentially problematic owing to differences in sample populations, a general examination of effect sizes (large versus small) may provide insight. For example, moderate to large therapeutic effect sizes were observed versus placebo for quetiapine 300 mg/day (0.78) and 600 mg/day (0.80) in this combined bipolar I cohort, similar to the overall cohort of bipolar I and II patients in BOLDER I (300 mg/day = 0.67; 600 mg/day = 0.81)[18] and in BOLDER II (300 mg/day = 0.61; 600 mg/day = 0.54).[20] Active comparator trials comparing quetiapine monotherapy to other treatments have not been reported to date, although they are needed. The pooled BOLDER study effect sizes are larger than those reported for olanzapine alone (0.32) and olanzapine/fluoxetine combination therapy (0.68) in patients with bipolar I disorder[17]; however, there are statistical limitations to this approach, in part because of the lack of data and direct head-to-head comparator trials. In a study of lamotrigine monotherapy in outpatients with bipolar I depression, effect sizes of 0.49 for lamotrigine 50 mg/day and 0.67 for lamotrigine 200 mg/day were observed by week 7 of treatment.[50] It should be noted that neither the lamotrigine nor olanzapine studies used an MMRM analysis as was used in the results presented here. Some studies have suggested that MMRM analyses may be more representative of the actual treatment effect than analysis of covariance with LOCF, as MMRM analyses use all available data to estimate the treatment effect in patients who withdrew prematurely.[51,52]

Analyses conducted to confirm that improvements in the MADRS scores were not due merely to sedative effects indicated that quetiapine has significant treatment-specific benefits on depressive symptoms independent of any sedating effects (as MADRS total scores improvement was similar in patients with and without sedation in the quetiapine-treated patients). Even though sedation and somnolence were the most common AEs leading to withdrawal, the rates of withdrawal were relatively low and comparable to those in most other trials in depressed subjects with bipolar disorder. Most discontinuations for sedation and somnolence occurred in the first week of treatment. There was a greater difference in change in MADRS total scores between the quetiapine and placebo groups in those patients without sedative effects than in those patients with sedative effects. One possible reason for this difference is the high response seen in the small group of patients in the placebo group with sedative effects (at week 8, change in MADRS total scores = –16.1, with 55.6% meeting MADRS response criteria; N = 36) compared to the placebo group without sedative effects (change in MADRS total scores = –9.7, with 35.5% meet-

ing MADRS response criteria; N = 186). Further analysis in other studies may be useful to better understand the impact of experiencing sedative effects in patients treated with placebo in bipolar depression, as the change in MADRS total scores was similar for subjects in both quetiapine arms of the combined trials in those with and without sedative effects.

The rates of response and remission in both quetiapine 300- and 600-mg/day groups were significantly superior to those of placebo, indicating a rapid and effective treatment response in these patients with bipolar I depression. The median time to first remission reported here (28 days for both quetiapine groups) was considerably shorter than that reported for olanzapine monotherapy (57 days), olanzapine/fluoxetine combination (42 days), or lamotrigine (41 days)[17,24] but similar to the olanzapine/fluoxetine combination (32 days) in the second study.[24] The median time to first response was also considerably shorter (22 days for both quetiapine groups) than that reported for olanzapine monotherapy (55 days) but was similar to that reported for olanzapine/fluoxetine combination in 2 separate studies (21 and 17 days).[17,24] In general, when predictors of response were assessed, the results indicated that treatment with quetiapine showed robust effects regardless of which subgroup was being examined.

In addition to improving the main symptoms of depression, both doses of quetiapine in this combined analysis were associated with significant improvements in anxiety symptoms, as shown by change in HAM-A total scores, indicating a broad effect of treatment, similar to the results of the BOLDER I study.[18,53] The use of lorazepam and zolpidem (allowed in the first 3 weeks of treatment) was low and similar between the treatment groups and therefore unlikely to have influenced the findings of this study.

Compared with placebo, both doses of quetiapine were more effective in improving overall quality of life in patients with bipolar I depression as measured by the Q-LES-Q SF. These improvements were observed by week 4 of treatment (first assessment). It is not too surprising that quetiapine also provided significantly superior improvements on the CGI-S, as these assessments, which were scored by the investigator, incorporate improvements in functioning, symptom severity, and global satisfaction.

Quetiapine was generally well tolerated. A smaller proportion of patients treated with quetiapine 300 mg/day withdrew from the study due to AEs than those treated with quetiapine 600 mg/day. Similar to the report of olanzapine and olanzapine/fluoxetine combination,[17] this study shows that quetiapine was not associated with treatment-emergent mania in patients with bipolar I depression. Changes in weight observed with quetiapine were moderate and did not result in withdrawal from the study. Weight gain in this study was at the lower end of the range of that seen with the use of some other atypical and typical antipsychotics, most of which show mean body weight gains of 2 to 9 kg.[54] These differences should be treated with caution, however, owing to the variability of study populations and study duration.

There is some initial evidence to suggest that patients with bipolar depression may benefit from psychoeducation that includes lifestyle interventions such as diet and exercise programs.[55] It has been shown in a small study of patients with major depression that increasing the level of exercise, for example, to 11 to 19 miles/week of walking or its equivalent, can potentially augment mood and anxiety treatment response and help with weight, lipid, and glucose control.[56] It has been recommended that all patients taking atypical antipsychotics have their weight and lipid and glucose levels monitored at baseline and at regular intervals thereafter.[57,58]

One limitation of the 2 studies is their relatively short duration. Efficacy and safety were not assessed beyond 8 weeks, and longer-term studies are required to assess maintenance of the treatment effect observed in this study. Although most of the analyses reported here were post hoc, quetiapine has been shown to be significantly more effective than placebo in 2 adequately powered and controlled monotherapy trials in bipolar depression in which the objectives were predefined.[18,20]

CONCLUSIONS

Quetiapine is more effective than placebo and generally well tolerated for the treatment of depressive episodes in patients diagnosed with bipolar I disorder. While the majority of bipolar depressed patients responded and even went into remission in this combined analysis, clinicians may still need to augment treatment with other mood stabilizing agents to achieve a maximum clinical response for some patients. Studies to further explore the place of combination therapy with quetiapine and other agents are needed in bipolar depressed patients. Further information on the longer term response to quetiapine monotherapy in the continuation and maintenance phases of bipolar disorder, as well as the longer term safety and tolerability, would also be valuable.

Drug names: aripiprazole (Abilify), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lorazepam (Ativan and others), olanzapine (Zyprexa), olanzapine/fluoxetine (Symbyax), quetiapine (Seroquel), zolpidem (Ambien and others).

Financial disclosure: **Dr. Weisler** has served as a consultant to the Agency for Toxic Substances and Disease Registry/Centers for Disease Control and Prevention, Bristol-Myers Squibb, Biovail, Eli Lilly, Wyeth Ayerst, Shire, Organon, sanofi-synthelabo, Forest, Solvay, Johnson & Johnson, Novartis, Otsuka, Corcept, Abbott, Pfizer, and GlaxoSmithKline; has received grant/research support from the National Institute of Mental Health, Pfizer, Eli Lilly, GlaxoSmithKline, Abbott, Merck, Organon, Biovail, Shire, sanofi-synthelabo, AstraZeneca, Janssen, Wyeth Ayerst, Solvay, Novartis,

Schwabe/Ingenix, Bristol-Myers Squibb, TAP, Synaptic, Elsai, UCB Pharma, Cephalon, Lundbeck, Forest, Pharmacia, Neurochem, Ciba-Geigy, Vela, Parke-Davis, Sandoz, Upjohn, MeidiciNova, SmithKline Beecham, Saegis, Corcept, New River, McNeil, Burroughs Welcome, and CoMentis; is a member of the speakers/advisory boards for Wyeth Ayerst, Solvay, GlaxoSmithKline, Eli Lilly, AstraZeneca, Cephalon, Biovail, Abbott, Forest, Bristol-Myers Squibb, Shire, Pfizer, Organon, and sanofi; and is a stock shareholder in Merck, Pfizer, Bristol-Myers Squibb, and Cortex. **Dr. Calabrese** has received grant/research support from the Department of Defense, the National Institute of Mental Health, the Health Resources Services Administration, The Cleveland Foundation, the National Alliance for Research on Schizophrenia and Depression, Repligen, The Stanley Medical Research Institute, Abbott, AstraZeneca, GlaxoSmithKline, Janssen, and Lilly; has been a member of speakers/advisory boards for Abbott, AstraZeneca, Bristol-Myers Squibb, the France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, and Solvay/Wyeth. **Dr. Thase** has served as a consultant to AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, GlaxoSmithKline, Janssen, MedAvante, Neuronetics, Novartis, Organon, Sepracor, Shire, Supernus, and Wyeth; has been a member of the speakers/advisory boards for AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly, GlaxoSmithKline, Organon, sanofi-aventis, and Wyeth. **Mr. Arvekvist** is an employee of AstraZeneca. **Drs. Stening** and **Paulsson** are employees of and stock shareholders in AstraZeneca. **Dr. Suppes** has received grant/research support or medications for clinical studies in the last 12 months from Abbott, AstraZeneca, GlaxoSmithKline, JDS Pharmaceuticals, the National Institute of Mental Health, Novartis, Pfizer, and the Stanley Medical Research Institute and has received royalties from Compact Clinicals. In prior activity, all of which ended by April 7, 2007, Dr. Suppes served on the speakers/advisory boards for AstraZeneca, Eli Lilly, GlaxoSmithKline, Novartis, and Pfizer.

REFERENCES

1. Keck PE Jr, Nelson EB, McElroy SL. Advances in the pharmacologic treatment of bipolar depression. Biol Psychiatry 2003;53:671–679
2. Angst J, Sellaro R. Historical perspectives and natural history of bipolar disorder. Biol Psychiatry 2000;48:445–457
3. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537
4. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. J Clin Psychiatry 2003 Jun;64(6):680–690
5. Altshuler LL, Gitlin MJ, Mintz J, et al. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. J Clin Psychiatry 2002 Sep;63(9):807–811
6. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60:261–269
7. Gladstone GL, Mitchell PB, Parker G, et al. Indicators of suicide over 10 years in a specialist mood disorders unit sample. J Clin Psychiatry 2001 Dec;62(12):945–951
8. Lopez P, Mosquera F, de Leon J, et al. Suicide attempts in bipolar patients. J Clin Psychiatry 2001 Dec;62(12):963–966
9. Nierenberg AA, Gray SM, Grandin LD. Mood disorders and suicide. J Clin Psychiatry 2001;62(suppl 25):27–30
10. Baldessarini RJ, Pompili M, Tondo L. Suicide in bipolar disorder: risks and management. CNS Spectr 2006;11:465–471
11. Hiroeh U, Appleby L, Mortensen PB, et al. Death by homicide, suicide, and other unnatural causes in people with mental illness: a population-based study. Lancet 2001;358:2110–2112
12. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder (revision). Am J Psychiatry 2002 Apr; 159(suppl 4):1–50
13. Suppes T, Dennehy EB, Hirschfeld RM, et al. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. J Clin Psychiatry 2005 Jul;66(7):870–886
14. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. J Clin Psychiatry 1999 Feb;60(2):79–88
15. Frye MA, Ketter TA, Kimbrell TA, et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. J Clin Psychopharmacol 2000;20:607–614
16. Sachs G, Altshuler L, Ketter T. Divalproex versus placebo for the treatment of bipolar depression. Paper presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikoloa, Hawaii
17. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003;60:1079–1088
18. Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005;162:1351–1360
19. Davis LL, Bartolucci A, Petty F. Divalproex in the treatment of bipolar depression: a placebo-controlled study. J Affect Disord 2005;85:259–266
20. Thase ME, Macfadden W, Weisler RH, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J Clin Psychopharmacol 2006; 26:600–609
21. Weisler RH, Cutler AJ, Ballenger JC, et al. The use of antiepileptic drugs in bipolar disorders: a review based on evidence from controlled trials. CNS Spectr 2006;11:788–799
22. Calabrese JR, Huffman RF, White RL, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-bind, placebo-controlled clinical trials. Bipolar Disord 2008;10:323–333
23. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
24. Brown EB, McElroy SL, Keck PE Jr, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. J Clin Psychiatry 2006 Jul;67(7):1025–1033
25. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–435
26. Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. J Clin Psychopharmacol 2008;28:13–20
27. Sajatovic M, Brescan DW, Perez DE, et al. Quetiapine alone and added to a mood stabilizer for serious mood disorders. J Clin Psychiatry 2001 Sep;62(9):728–732
28. Sajatovic M, Mullen JA, Sweitzer DE. Efficacy of quetiapine and risperidone against depressive symptoms in outpatients with psychosis. J Clin Psychiatry 2002 Dec;63(12):1156–1163
29. Suppes T, Hirschfeld RM, Vieta E, et al. Quetiapine for the treatment of bipolar II depression: analysis of data from two randomized, double-blind, placebo-controlled studies. World J Biol Psychiatry 2007 May 11:1–14 [Epub ahead of print]
30. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press; 1994
31. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
32. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
33. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
34. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull 1993;29:321–326
35. Buysse DJ, Reynolds CF III, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213
36. Sheehan DV. The Anxiety Disease. New York, NY: Scribner's; 1983
37. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
38. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
39. Bowden CL, Davis J, Morris D, et al. Effect size of efficacy measures comparing divalproex, lithium and placebo in acute mania. Depress Anxiety 1997;6:26–30
40. Grunze H, Kasper S, Goodwin G, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of

bipolar disorders, pt 1: treatment of bipolar depression. World J Biol Psychiatry 2002;3:115–124
41. Yatham LN, Kennedy SH, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. Bipolar Disord 2006;8:721–739
42. Fountoulakis KN, Vieta E, Siamouli M, et al. Treatment of bipolar disorder: a complex treatment for a multi-faceted disorder. Ann Gen Psychiatry 2007 Oct;6:27
43. Baldessarini RJ, Tondo L. Suicide risk and treatments for patients with bipolar disorder. JAMA 2003;290:1517–1519
44. Chen YW, Dilsaver SC. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. Biol Psychiatry 1996;39:896–899
45. Goodwin F, Jamison K. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990
46. Harris EC, Barraclough B. Suicide as an outcome for mental disorders: a meta-analysis. Br J Psychiatry 1997;170:205–228
47. Simpson SG, Jamison KR. The risk of suicide in patients with bipolar disorders. J Clin Psychiatry 1999;60(suppl 2):53–56, discussion 75–76, 113–116
48. Dalton EJ, Cate-Carter TD, Mundo E, et al. Suicide risk in bipolar patients: the role of co-morbid substance use disorders. Bipolar Disord 2003;5:58–61
49. US Food and Drug Administration. FDA Alert. Suicidality and antiepileptic drugs. Jan 31, 2008. Available at: http://www.fda.gov/cder/drug/infopage/antiepileptics. Updated Feb 1, 2008. Accessed Feb 25, 2008
50. Grunze H. Reevaluating therapies for bipolar depression. J Clin Psychiatry 2005;66(suppl 5):17–25
51. Mallinckrodt CH, Clark SW, Carroll RJ, et al. Assessing response profiles from incomplete longitudinal clinical trial data under regulatory considerations. J Biopharm Stat 2003;13:179–190
52. Mallinckrodt CH, Raskin J, Wohlreich MM, et al. The efficacy of duloxetine: a comprehensive summary of results from MMRM and LOCF_ANCOVA in eight clinical trials. BMC Psychiatry 2004 Sep;4:26
53. Hirschfeld RM, Weisler RH, Raines SR, et al. Quetiapine in the treatment of anxiety in patients with bipolar I or II depression: a secondary analysis from a randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2006 Mar;67(3):355–362
54. Baptista T, Kin NM, Beaulieu S, et al. Obesity and related metabolic abnormalities during antipsychotic drug administration: mechanisms, management and research perspectives. Pharmacopsychiatry 2002;35: 205–219
55. Colom F, Vieta E, Reinares M, et al. Psychoeducation efficacy in bipolar disorders: beyond compliance enhancement. J Clin Psychiatry 2003 Sep;64(9):1101–1105
56. Trivedi MH, Greer TL, Grannemann BD, et al. Exercise as an augmentation strategy for treatment of major depression. J Psychiatr Pract 2006; 12:205–213
57. Masand PS, Culpepper L, Henderson D, et al. Metabolic and endocrine disturbances in psychiatric disorders: a multidisciplinary approach to appropriate atypical antipsychotic utilization. CNS Spectr 2005 Oct;10(suppl 14):1–15
58. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27:596–601