Clinical Highlights in Bipolar Depression: Focus on Atypical Antipsychotics

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Despite the considerable burden of bipolar depression, the treatment of this debilitating phase of bipolar disorder is suboptimally addressed by currently available pharmacologic options. Consequently, there is a need for the development of new treatment options with enhanced efficacy and tolerability. Evidence of antidepressant efficacy for some of the atypical antipsychotics in the treatment of bipolar depression has recently emerged. The findings of a large-scale, placebo-controlled, double-blind, randomized clinical study of olanzapine alone and in combination with fluoxetine, and a similar study of quetiapine monotherapy, suggest that some of the atypical antipsychotics may be efficacious in treating depressive symptoms in patients with bipolar I disorder. Subpopulation analyses suggest that quetiapine monotherapy and the olanzapine plus fluoxetine combination appear to be effective in treating depression in patients with a rapid-cycling course. The magnitude of improvement in depressive symptoms in the bipolar I population appears to be larger for quetiapine monotherapy compared with either olanzapine or olanzapine plus fluoxetine; however, the limitations of such a cross-study comparison are acknowledged. Both olanzapine monotherapy and combination therapy, as well as quetiapine monotherapy, were well tolerated. The overall incidence of treatment-emergent mania was low and comparable with placebo in both studies. Somnolence, weight gain, increased appetite and nonfasting glucose and cholesterol levels were more commonly reported in patients treated with olanzapine monotherapy or combination therapy compared with placebo. Dry mouth, sedation/somnolence, dizziness, and constipation were more commonly associated with quetiapine treatment. Large, controlled studies are needed to determine whether other psychotropic agents have antidepressant properties that would make them suitable for use in patients with bipolar depression. In addition, direct comparison of the regimens used in the current study should determine whether the differences evident between them can be confirmed.

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The burden of bipolar depression is greater than that of bipolar mania in terms of the time spent by patients in the depressive phase of this illness.[1–5] Patients with bipolar I disorder can expect to spend 3 times as long experiencing acute and subsyndromal depressive symptoms as manic/hypomanic symptoms,[1] and patients with bipolar II disorder experience an even greater proportion of depressive symptoms than hypomanic symptoms.[2] Compared with bipolar mania, bipolar depression is associated with an increased risk of suicide[6–9] and impaired functioning,[10] even when the symptoms do not meet threshold criteria for a major depressive episode.[6] Despite the considerable burden of bipolar depression, the treatment of this phase of bipolar disorder has not been as widely studied as bipolar mania and is suboptimally addressed by currently available pharmacologic options.

Treatment guidelines of the American Psychiatric Association[11] and the 2004 Expert Consensus Guideline Series[12] for the management of bipolar depression recommend either lithium (with substantial clinical confidence) or lamotrigine (with moderate clinical confidence) as first-line monotherapy for patients with bipolar depression.

Table 1. Baseline Demographics and Disease Characteristics of Patients in 8-Week, Double-Blind, Randomized, Placebo-Controlled Clinical Studies of Olanzapine, Olanzapine Plus Fluoxetine, and Quetiapine for the Treatment of Bipolar Depression (intent-to-treat population)[a,b]

Characteristic	Olanzapine (5–20 mg/d), N = 370[16]	Olanzapine (6–12 mg/d) Plus Fluoxetine (25–50 mg/d), N = 86[16]	Placebo, N = 377[16]	Quetiapine (600 mg/d), N = 170[17]	Quetiapine (300 mg/d), N = 172[17]	Placebo, N = 169[17]
Age, mean ± SD, y	42.2 ± 12.5	40.3 ± 13.0	41.7 ± 12.4	37.3 ± 11.4	36.6 ± 11.2	38.3 ± 11.1
Gender, %						
Male	37.6	32.6	37.4	41.8	45.9	37.9
Female	62.4	67.4	62.6	58.2	54.1	62.1
Baseline symptom severity score, mean						
MADRS	32.6	30.8	31.3	30.3	30.4	30.6
HAM-D-17	NR	NR	NR	24.7	24.5	24.6
HAM-A	17.1	15.8	16.7	18.7	18.6	18.9
Rapid-cycling course, %	38.4	39.5	35.0	18.2	24.4	20.7

[a]Data from Tohen et al[16] and Calabrese et al.[17] [b]Patient numbers represent all randomly assigned patients.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, NR = not reported.

Other practice guidelines consider that unimodal antidepressants may be indicated in certain subgroups as first-line therapy.[13] However, most guidelines acknowledge that traditional antidepressant monotherapy, used in the treatment of unipolar depression, is associated with a risk of treatment-emergent mania and cycle acceleration in bipolar depression and is therefore not recommended. Consequently, it is generally recommended that unimodal antidepressants should always be coadministered with a mood stabilizer when used in patients with bipolar depression.[11,13,14] Antidepressant use in the management of bipolar depression is reviewed in more detail elsewhere in this supplement.[15]

Given that current therapy does not adequately address the needs of all patients with bipolar depression, the development of new treatment options with enhanced efficacy and tolerability is required. Evidence of the antidepressant efficacy of several new options in the treatment of bipolar depression has recently emerged.[16,17] The results of large-scale, placebo-controlled clinical trials of olanzapine[16] and quetiapine[17] in bipolar depression have been reported. We review the results of these pivotal studies, attempt to compare analogous outcome variables, and discuss the implications for clinical practice.

OLANZAPINE AND OLANZAPINE-FLUOXETINE FOR THE TREATMENT OF BIPOLAR DEPRESSION

The atypical antipsychotic olanzapine has been shown to be effective in the treatment of acute bipolar mania.[18–20] In addition, there is some evidence that olanzapine may improve depressive symptoms associated with schizophrenia[21] and psychotic depression.[22] Olanzapine has also been shown to be effective in the prevention of relapse into either depression or mania.[23,24]

The efficacy and tolerability of olanzapine monotherapy were assessed in 2 large-scale, 8-week, placebo-controlled, double-blind, randomized clinical studies,[16] the results of which were pooled. Smaller groups of patients in each study were treated with olanzapine in combination with the selective serotonin reuptake inhibitor (SSRI) fluoxetine for exploratory purposes, as this combination was previously found to be effective in a small number of patients with treatment-resistant unipolar depression.[25]

Study Method

A pooled total of 833 adults with bipolar I depression (DSM-IV criteria and a Montgomery-Asberg Depression Rating Scale [MADRS] score ≥ 20) was randomly assigned in a 4:4:1 allocation to receive either olanzapine monotherapy (N = 370), placebo (N = 377), or olanzapine plus fluoxetine (N = 86) for up to 8 weeks.[16] Patients with bipolar II disorder were excluded. A flexible dosing schedule was followed, in which therapy was initiated at 5 mg/day for olanzapine monotherapy and adjusted by 5-mg/day increments, if needed, up to a maximum of 20 mg/day. For the olanzapine-fluoxetine combination, therapy was initiated at 6 mg/day of olanzapine and 25 mg/day of fluoxetine, but could be changed to 6 and 50 mg/day or 12 and 50 mg/day after at least 1 day at each dose. Depressive symptoms were assessed at weeks 1, 2, 3, 4, 6, and 8 using the MADRS. The primary measure of efficacy was the mean change from baseline to last assessment in the MADRS total score and was analyzed using both the last-observation-carried-forward (LOCF) strategy and the mixed-effect model repeated-measures (MMRM) method. Table 1 details the baseline demographics and disease characteristics of the pooled study population.

Results

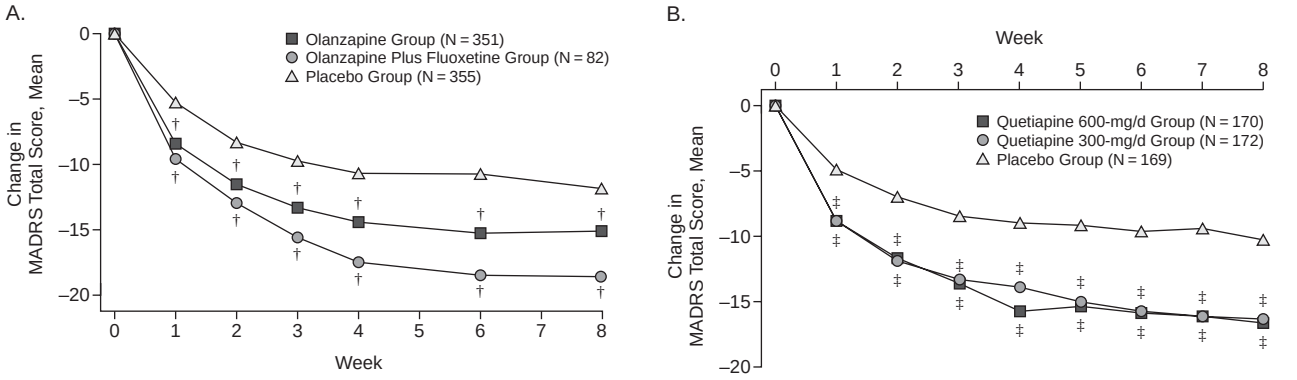
MADRS total score. At week 8, significant improvements in MADRS total score were observed with olanzapine (mean ± SE improvement of 15.0 ± 0.7 points;

Table 2. Change From Baseline to Endpoint in the MADRS, HAM-D-17, and HAM-A Total Scores and Response and Remission Rates in 8-Week, Double-Blind, Randomized, Placebo-Controlled Clinical Studies of Olanzapine, Olanzapine Plus Fluoxetine, and Quetiapine for the Treatment of Bipolar Depression[a]

Efficacy Measure	Olanzapine (5–20 mg/d)[16]	Olanzapine (6–12 mg/d) Plus Fluoxetine (25–50 mg/d)[16]	Placebo[16]	Quetiapine (600 mg/d)[17]	Quetiapine (300 mg/d)[17]	Placebo[17]
MADRS, mean ± SE score change	–15.0 ± 0.7**	–18.5 ± 1.3***	–11.9 ± 0.8	–16.73 ± 0.91***	–16.39 ± 0.91***	–10.26 ± 0.91
HAM-D-17, mean ± SE score change	NR	NR	NR	–13.84 ± 0.67***	–3.38 ± 0.66***	–8.54 ± 0.67
HAM-A, mean ± SE score change	–5.5 ± 0.4**	–7.0 ± 1.0***	–3.5 ± 0.4	–8.75 ± 0.59***	–8.64 ± 0.58***	–5.54 ± 0.58
Response[b] rate, %	39.0*	56.1***	30.4	58.2***	57.6***	36.1
Remission[c] rate, %	32.8*	48.8***	24.5	52.9***	52.9***	28.4

[a]Data from Tohen et al[16] and Calabrese et al.[17] [b]Defined as ≥ 50% improvement in the MADRS total score from baseline to endpoint (also completion of at least 4 weeks of treatment in the olanzapine study). [c]Defined as a MADRS total score of ≤ 12 points (also completion of at least 4 weeks of treatment in the olanzapine study).
*p < .05 versus placebo. **p < .01 versus placebo. ***p < .001 versus placebo.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, NR = not reported.

Figure 1. (A) Mean Change From Baseline to Endpoint in the MADRS Score Among Adult Patients With Bipolar Depression Treated With Olanzapine, Olanzapine Plus Fluoxetine, or Placebo for up to 8 Weeks[a,b] and (B) Mean Change From Baseline to Endpoint in the MADRS Score Among Adult Patients With Bipolar Depression Treated With Quetiapine (300 mg/d or 600 mg/d) or Placebo for up to 8 Weeks[c,d]



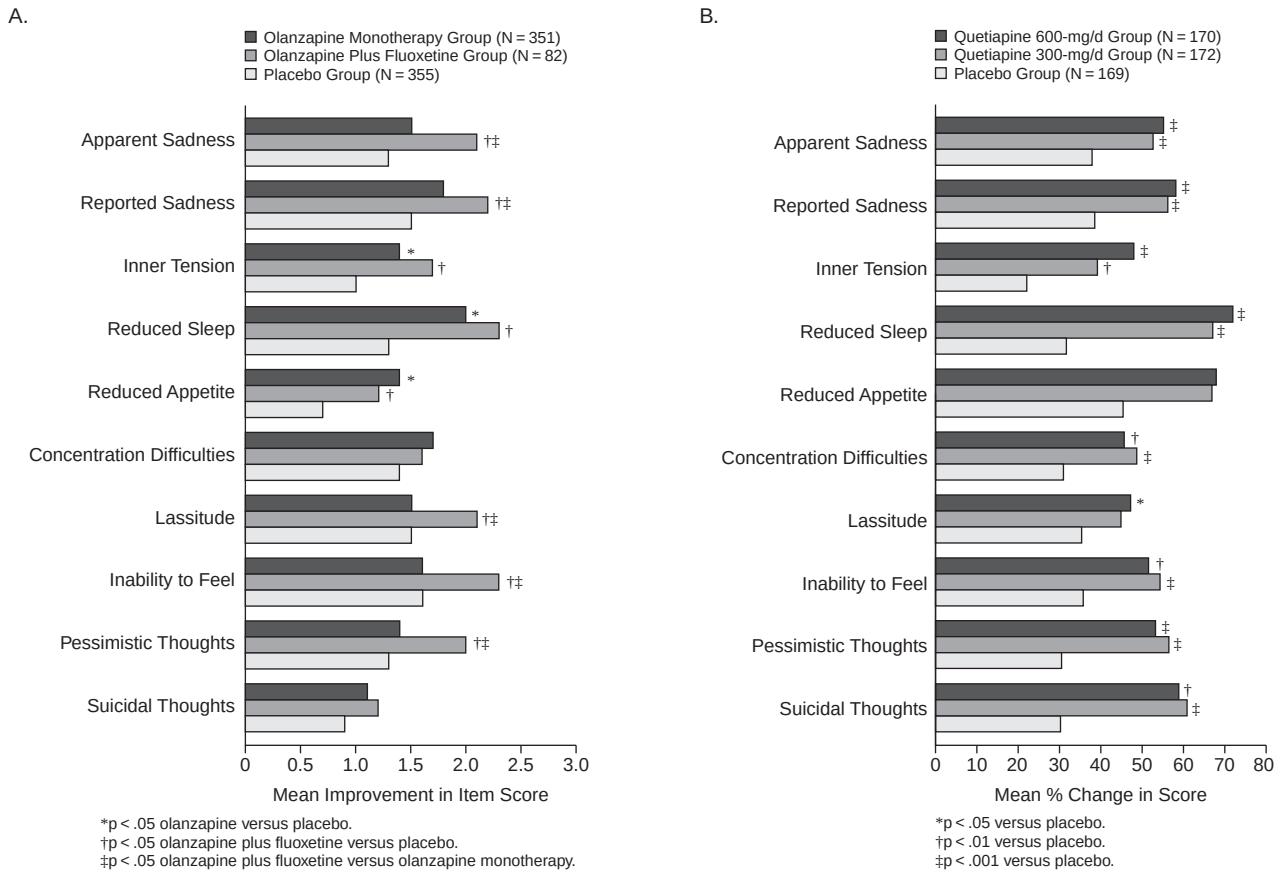
[a]Adapted with permission from Tohen et al.[16] [b]Intent to treat, mixed-effect model repeated measures. [c]Reprinted with permission from Calabrese et al.[17] [d]Intent to treat, last observation carried forward.
†p < .001 versus placebo for olanzapine and olanzapine-fluoxetine throughout the study. ‡p < .001 versus placebo for quetiapine throughout the study.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

p = .002 vs. placebo) and the olanzapine-fluoxetine combination (mean ± SE improvement of 18.5 ± 1.3 points; p < .001 vs. placebo) groups compared with placebo (mean ± SE improvement of 11.9 ± 0.8 points; Table 2). In the pooled analysis, significance over placebo was attained by both olanzapine monotherapy and olanzapine-fluoxetine by week 1 and was maintained until study end (Figure 1A). From weeks 4 to 8, the olanzapine-fluoxetine combination was also superior to olanzapine monotherapy.

Effect size. The effect size is a measure of the magnitude of treatment effect over placebo (improvement over placebo divided by pooled standard deviation). An effect size of less than 0.4 is considered small, 0.4 to 0.79 is considered medium and is correlated with clinical improvement, and an effect size greater than 0.79 is considered large.[26,27] Based on an MMRM analysis of the improvement in the MADRS scores, the effect size was 0.32 for olanzapine and 0.68 for the olanzapine-fluoxetine combination.

MADRS individual items. The MMRM analysis of MADRS items revealed a significant improvement versus placebo in 3 of 10 items with olanzapine monotherapy (inner tension, reduced sleep, and reduced appetite) compared with 8 of 10 items for the olanzapine-fluoxetine combination (all items except concentration difficulties and suicidal thoughts) (Figure 2A). Olanzapine monotherapy did not separate from placebo in 3 of the core symptoms of depression: apparent sadness, reported sadness, and suicidal thoughts.

Figure 2. (A) Mean Change in MADRS Item Scores From Baseline to Endpoint Among Adult Patients With Bipolar Depression Treated With Olanzapine, Olanzapine Plus Fluoxetine, or Placebo for up to 8 Weeks[a,b] and (B) Mean Change in MADRS Item Scores From Baseline to Endpoint Among Adult Patients With Bipolar Depression Treated With Quetiapine (300 mg/d or 600 mg/d) or Placebo for up to 8 Weeks[c,d]



[a]Data from Tohen et al.[16] [b]Intent to treat, mixed-effect model repeated measures. [c]Reprinted with permission from Calabrese et al.[17] [d]Intent to treat, last observation carried forward.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Using a LOCF analysis, the olanzapine-fluoxetine combination was superior to placebo for all items, while olanzapine monotherapy was significantly superior to placebo for 6 of 10 items (all except concentration difficulties, lassitude, inability to feel, and pessimistic thoughts) (J.C., unpublished data). The olanzapine-fluoxetine combination was superior to olanzapine alone in improvement of 6 of 10 items (all except reduced sleep, reduced appetite, concentration difficulties, and suicidal thoughts).

Response and remission. Significantly more patients in the active treatment arms achieved a response (≥ 50% improvement in MADRS total score from baseline and completion of ≥ 4 weeks of the study) than in the placebo arm (Table 2). Patients treated with olanzapine alone achieved a significantly greater response (137 [39.0%] of 351 patients) to treatment compared with placebo (108 [30.4%] of 355 patients; p = .02). For patients treated with the olanzapine-fluoxetine combination, the response rate was 46 (56.1%) of 82 patients, significantly higher than that observed with either olanzapine monotherapy (p = .006) or placebo (p < .001). Median time to response was significantly shorter for patients treated with the olanzapine-fluoxetine combination (21 days) than for either olanzapine monotherapy (55 days) or placebo (59 days). A similar pattern was observed when remission (defined as a MADRS total score of ≤ 12 and completion of ≥ 4 weeks of the study) rates were examined, with patients treated with the olanzapine-fluoxetine combination achieving higher rates of remission than olanzapine monotherapy or placebo patients (Table 2).

Anxiety symptoms. Anxiety symptoms assessed using the Hamilton Rating Scale for Anxiety (HAM-A) significantly improved with both active treatments compared with placebo (Table 2). This was the only efficacy measure for which the olanzapine-fluoxetine combination was not significantly superior to olanzapine monotherapy.

Quality of life. Health-related quality of life (QOL), measured by changes in dimension and component summary scores on Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and total score on the Quality of Life in Depression Scale, indicated that olanzapine and the olanzapine-fluoxetine combination significantly improved QOL compared with placebo ($p < .05$).[28]

Rapid-cycling patients. A secondary analysis revealed that patients with a history of rapid cycling who were treated with the olanzapine-fluoxetine combination (N = 37) experienced a greater improvement in depressive symptoms ($p < .01$ at end of study) than olanzapine- or placebo-treated patients (N = 140 and 138, respectively).[29]

Summary. Overall, the antidepressant effect of the olanzapine-fluoxetine combination was significantly greater than that of olanzapine alone, while both arms were superior to placebo in most reported efficacy measures in the pooled analysis of the 2 studies. While the magnitude of the clinical effect with olanzapine monotherapy was small, it became moderately large when olanzapine was combined with the antidepressant fluoxetine. The U.S. Food and Drug Administration has approved the combination of olanzapine and fluoxetine for the treatment of bipolar depression.[30]

QUETIAPINE FOR THE TREATMENT OF BIPOLAR DEPRESSION

Quetiapine has demonstrated efficacy in the treatment of bipolar mania, both as monotherapy and in combination with other mood stabilizers, such as lithium.[31,32] Several small, randomized, and open-label studies have suggested that quetiapine may be effective in the treatment of depressive symptoms associated with a number of psychotic and mood disorders, including bipolar disorder,[33] rapid-cycling bipolar disorder,[34,35] and adolescent mania.[36]

Study Method

The efficacy, safety, and tolerability of quetiapine as monotherapy for bipolar I and II depression have been assessed in a large-scale, 8-week, placebo-controlled, randomized clinical study.[17,37] This study included patients with bipolar I and II disorder, with or without rapid cycling.

A total of 542 adult outpatients (N = 360 bipolar I, N = 182 bipolar II; DSM-IV criteria) were randomly assigned to 8 weeks of double-blind treatment with quetiapine (fixed dose of 600 mg/day or 300 mg/day) or placebo in a 1:1:1 ratio. Patients were required to have a 17-item Hamilton Rating Scale for Depression (HAM-D-17) score ≥ 20, a HAM-D-17 item 1 score ≥ 2, and a Young Mania Rating Scale (YMRS) score ≤ 12. Depressive symptoms were assessed at weekly intervals using the MADRS scale. The primary efficacy assessment was the mean change from baseline to last assessment in the MADRS total score and was analyzed using both LOCF and MMRM methods; effect size was calculated using the MMRM method. Table 1 details the baseline demographics and disease characteristics of the study population.

Results

MADRS total score. Patients with either bipolar I or II depression treated with quetiapine experienced significant and sustained improvement in their overall depressive symptoms as measured by the MADRS. Significant improvements compared with placebo were observed as early as week 1 of treatment and at all subsequent assessments to week 8 (Figure 1B).[17]

Effect size. The effect size (MMRM), based on improvement in the MADRS scores, was 0.81 for quetiapine 600 mg/day and 0.67 for quetiapine 300 mg/day.

MADRS individual items. Using the LOCF strategy, MADRS item analysis revealed significant improvement compared with placebo ($p < .05$) in 9 of 10 and 8 of 10 items with quetiapine 600- and 300-mg/day monotherapy, respectively, including the core symptoms of depression (apparent sadness, reported sadness, inner tension, and suicidal thoughts) (Figure 2B). Both doses of quetiapine were more effective than placebo in reducing suicidal thoughts.

Results observed on the MADRS were confirmed by assessments using the HAM-D-17, which also indicated a significant improvement in depressive symptoms with quetiapine (600 or 300 mg/day) from week 1 to end of study (Table 2).

Response and remission. Significantly more patients responded to treatment (response defined as ≥ 50% reduction from baseline MADRS total score) and achieved remission (defined as MADRS total score ≤ 12) with quetiapine than with placebo (Table 2). In total, 99/170 (58.2%) and 99/172 (57.6%) of patients treated with quetiapine 600 mg/day and 300 mg/day, respectively, responded at the end of the study (week 8), which was significantly greater than in the placebo group (61 [36.1%] of 169 patients; $p < .001$). A similar pattern was observed when remission rates were examined, with a greater proportion of patients who received either dose of quetiapine (600 mg/day or 300 mg/day) achieving remission at final assessment (90/170 [52.9%] and 91/172 [52.9%], respectively) compared with 48 (28.4%) of 169 patients who received placebo ($p < .001$). The median time to response and remission was significantly shorter for quetiapine groups compared with placebo. The median time to response for quetiapine-treated patients was 22 days in both quetiapine groups compared with 36 days in the placebo group ($p < .001$ for both doses). The median time to symptomatic remission followed a similar pattern, with patients treated with 600 mg/day and 300 mg/day of quetiapine achieving remission in 27 and 29 days, respectively, compared with 65 days in the placebo arm ($p < .001$ for both doses).

Anxiety symptoms. Secondary efficacy analyses revealed significant improvements in anxiety symptoms,

measured using the HAM-A. Separation from placebo was observed as early as week 1 with both doses of quetiapine ($p < .05$) (Table 2) and maintained through to the end of treatment ($p < .001$).

Quality of life. Health-related quality of life at week 8 (measured by the Quality of Life Enjoyment and Satisfaction Questionnaire) and quality of sleep after 8 weeks (measured using the Pittsburgh Sleep Quality Index) were also significantly improved[17] with both doses of quetiapine compared with placebo ($p < .001$).

Patients with bipolar I depression. As this study included a mixed population of patients with bipolar I or II disorder, exploratory subanalyses in the patients with bipolar I disorder were conducted that allow a more appropriate comparison to the population of patients in the studies by Tohen et al.[16,23] As reported for the overall study population, significant improvements were seen in the mean MADRS total score from baseline to last assessment (quetiapine 600 mg/day, –18.05 points, and quetiapine 300 mg/day, –16.91 points) compared with placebo (–9.24 points; $p < .001$ for both using LOCF) for patients with a diagnosis of bipolar I disorder (MMRM effect sizes 1.09 and 0.91 for the 600- and 300-mg/day groups, respectively).[17]

Rapid-cycling patients. Significant improvements were also observed in the mean MADRS total scores of all patients with a rapid-cycling disease course compared with placebo, regardless of the presence of a rapid-cycling course of illness (–17.7, –18.6 vs. –9.9 in the 600 mg/day quetiapine, 300 mg/day quetiapine, and placebo groups, respectively; $p < .01$ for both quetiapine doses vs. placebo).

Summary. Overall, these data demonstrate that quetiapine monotherapy is effective in bipolar depression and has a rapid onset of action (week 1) at both doses tested. Efficacy in the depressive episodes of patients with bipolar I or II disorder, either with or without a rapid-cycling disease course, was demonstrated with quetiapine.

SAFETY AND TOLERABILITY

Treatment-Emergent Mania

Any treatment for bipolar depression should not induce patients into a manic episode. The risk of treatment-emergent mania is therefore an important safety consideration in the management of bipolar depression. The incidence of treatment-emergent mania was assessed in both the olanzapine and quetiapine studies using the YMRS. In the olanzapine study, treatment-emergent mania was defined as a YMRS score < 15 at baseline and ≥ 15 at any point thereafter; all patients with treatment-emergent mania during weeks 1 through 3 were withdrawn from treatment. The quetiapine study defined treatment-emergent mania as a YMRS score ≥ 16 points at 2 consecutive visits or at final visit, or as an adverse event of mania/hypomania as judged by the investigator. Such patients were not withdrawn from treatment. The overall incidence of treatment-emergent mania or hypomania was low and comparable with placebo for both olanzapine and quetiapine. In the olanzapine study, the rates of treatment-emergent mania were 6.7% in the placebo group compared with 5.7% for the olanzapine monotherapy group and 6.4% for the olanzapine-fluoxetine combination group. In the quetiapine study, the rates of treatment-emergent mania were 2.2% for quetiapine 600 mg/day, 3.9% for quetiapine 300 mg/day, and 3.9% for placebo.

Adverse Events

In the olanzapine and olanzapine-fluoxetine study groups, somnolence, weight gain, increased appetite, dry mouth, asthenia, and diarrhea were the treatment-related adverse events occurring in 10% or more and at twice the rate of placebo for any treatment group.[16] By similar criteria, in patients treated with quetiapine, dry mouth, sedation, somnolence, dizziness, and constipation were the most frequently reported adverse events[17]; however, these were not all confirmed as treatment related. Table 3 details the most frequently reported adverse events in both studies.

Weight gain. Significantly more patients treated with either olanzapine monotherapy or the olanzapine-fluoxetine combination reported weight gain as an adverse event compared with placebo (Table 3; $p < .001$ for both), and a significantly greater proportion of patients who received olanzapine experienced potentially clinically relevant weight increases (≥ 7% increase from baseline) than those patients who received placebo ($p < .001$ for both). Moreover, there was no difference between the olanzapine and olanzapine-fluoxetine groups either in actual weight gain (2.59 kg and 2.79 kg, respectively) or in the proportion of patients with potentially clinically significant gains (Table 3). In comparison, weight gain was not one of the most frequent adverse events reported among patients treated with quetiapine (1.6 kg and 1.0 kg for 600- and 300-mg/day doses, respectively). In addition, nonfasting glucose levels were significantly higher for the olanzapine and olanzapine-fluoxetine groups than among patients who received placebo.[16] With quetiapine treatment, fasting glucose levels did increase compared with placebo, but significance testing was not carried out.[17] The results from these 2 placebo-controlled studies suggest that patients treated with olanzapine may be more susceptible to developing multiple components of metabolic syndrome than those treated with quetiapine; however, this requires further study.

Withdrawals due to adverse events. In the olanzapine studies,[16] fewer patients treated with placebo (5.0%) withdrew from treatment due to adverse events compared with patients treated with olanzapine monotherapy (9.2%), and fewer patients treated with the olanzapine-fluoxetine combination (2.3%) discontinued compared with olanzapine monotherapy. In the quetiapine study,[17] adverse events

Table 3. Incidence of Common Adverse Events Occurring in 8-Week, Double-Blind, Randomized, Placebo-Controlled Clinical Studies of (A) Olanzapine, Olanzapine Plus Fluoxetine, and (B) Quetiapine for the Treatment of Bipolar Depression[a,b]

(A) Adverse Event, %[16]	Olanzapine (5–20 mg/d)	Olanzapine (6–12 mg/d) Plus Fluoxetine (25–50 mg/d)	Placebo
Somnolence	28.1	20.9	12.5
Weight gain	17.3	17.4	2.7
Increased appetite	13.5	12.8	5.0
Dry mouth	11.1	16.3	6.1
Asthenia	9.7	12.8	3.2
Diarrhea	6.5	18.6	6.6
(B) Adverse Event, %[17]	**Quetiapine (600 mg/d)**	**Quetiapine (300 mg/d)**	**Placebo**
Dry mouth	40.6	44.1	7.8
Sedation	32.2	29.6	6.1
Somnolence	24.4	27.4	8.3
Dizziness	22.8	16.8	8.3
Constipation	11.1	11.7	4.4

[a]Data from Tohen et al.[16] and Calabrese et al.[17] [b]Common adverse events were those that occurred in > 10% of patients and at more than twice the rate of placebo.

were cited as the main reason for withdrawal from treatment in 26.1% of patients treated with quetiapine 600 mg/day, 16.0% of patients treated with quetiapine 300 mg/day, and 8.8% of patients who received placebo. The majority of these withdrawals were due to somnolence or sedation and occurred during the first week of the study.

OTHER ATYPICAL ANTIPSYCHOTICS

No large double-blind, randomized, controlled study data examining efficacy among adults with bipolar depression have been published to date for any other atypical antipsychotic. However, there is some evidence in the literature that risperidone and other agents may improve depressive symptoms in patients with bipolar disorder.[38] Risperidone significantly improved depressive symptoms, as measured using the HAM-D, among 541 adult patients with bipolar disorder or schizoaffective disorder.[39] Almost 70% of patients with a baseline HAM-D score ≥ 17 points achieved a symptomatic response defined as a ≥ 50% decrease in the mean HAM-D total score.[39] Two small studies[40,41] have suggested that aripiprazole may be effective in combination with an antidepressant in the management of treatment-resistant depression. In addition, in a randomized controlled study,[42] aripiprazole prolonged the time to relapse of manic, but not depressive, symptoms among adult patients with bipolar I disorder. There are no reports of the efficacy of ziprasidone in the treatment of depressive symptoms in patients with bipolar disorder and just one report of a small-scale open study examining the efficacy of this agent in the treatment of SSRI-resistant major depressive disorder in combination with existing SSRI therapy.[43]

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

While cross-study comparisons should be viewed with caution, the results of these placebo-controlled, 8-week studies suggest that there may be important clinical differences between olanzapine and quetiapine in their efficacy in the treatment of bipolar depression. While both agents provided significant improvements in depressive symptoms compared with placebo, the antidepressant effect size (based on an MMRM analysis of the primary efficacy measure from each study) for olanzapine monotherapy was small, and the olanzapine-fluoxetine combination proved more effective than olanzapine monotherapy across almost all efficacy measures reported in the study.[16] The observed antidepressant effect size for either dose of quetiapine among patients with bipolar I depression (1.09 and 0.91 for the 600- and 300-mg/day doses, respectively)[17] exceeded the effect size observed for either olanzapine monotherapy (0.32) or the olanzapine-fluoxetine combination (0.68).[16] Assessment of the clinical effect in these studies indicates that olanzapine monotherapy had a small magnitude of effect, but this became moderately large when olanzapine was combined with the antidepressant fluoxetine. With quetiapine monotherapy, the magnitude of effect was large regardless of the dose used. These data suggest that quetiapine monotherapy may be superior to an olanzapine-fluoxetine combination in treating depressive symptoms in patients with bipolar I disorder.

In addition, response and remission rates were comparable between the olanzapine-fluoxetine combination and quetiapine monotherapy (at either dose) and markedly higher than were achieved with olanzapine monotherapy (Table 2). It should be noted, however, that the definitions for response and remission differed slightly between the 2 studies.

Direct comparisons between olanzapine, olanzapine-fluoxetine combination, and quetiapine in future studies will likely identify whether the apparent differences evident from this cross-study comparison can be confirmed.

Despite the considerable burden of bipolar depression in terms of both increased risk of suicide and impaired functioning, the treatment of this debilitating component of bipolar disorder has not been as widely studied as that of bipolar mania. As discussed in this review, evidence is emerging for the efficacy of the atypical antipsychotics, either as monotherapy or in combination with unimodal antidepressants, in the management of this vulnerable patient group.

Additional evidence from small-scale studies in subpopulations of patients with bipolar disorder and those with a variety of mood disorders suggests that other psychotropic agents may also improve depressive symptoms.[40,41] Large, controlled studies are now needed to determine whether these agents have antidepressant properties that would make them suitable for use in patients with bipolar depression.

Drug names: aripiprazole (Abilify), fluoxetine (Prozac and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbyax), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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