A Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Quetiapine or Lithium as Monotherapy for Mania in Bipolar Disorder

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Objective: To evaluate the efficacy and tolerability of quetiapine monotherapy versus placebo for the treatment of mania associated with bipolar disorder.

Method: In an international, multicenter, double-blind, parallel-group, 12-week study, patients with a DSM-IV diagnosis of bipolar I disorder (manic episode) were randomly assigned to treatment with quetiapine (flexibly dosed up to 800 mg/day), placebo, or lithium. The primary efficacy measure was change from baseline in Young Mania Rating Scale (YMRS) score at day 21. Data were gathered from April 2001 to May 2002.

Results: More patients in the quetiapine (72/107) and lithium (67/98) groups completed the study compared with the placebo group (35/97). Improvement (reduction) in YMRS score was significantly greater for quetiapine than placebo at day 7 (–8.03 vs. –4.89; $p < .01$), and the difference between groups continued to increase over time to day 21 (–14.6 vs. –6.7; $p < .001$) and to endpoint at day 84 (–20.3 vs. –9.0; $p < .001$). Significantly more quetiapine patients compared with placebo patients fulfilled YMRS response criteria at day 21 (53.3% vs. 27.4%; $p < .001$) and at day 84 (72.0% vs. 41.1%; $p < .001$). Quetiapine was also superior to placebo in efficacy at day 21 and day 84 by all secondary measures. Lithium-treated patients improved significantly compared with placebo patients and similarly to quetiapine-treated patients on the primary efficacy measure. The most common adverse events for quetiapine were dry mouth, somnolence, and weight gain, while lithium was associated with tremor and insomnia. The quetiapine and placebo groups had similar, low levels of extrapyramidal symptom–related adverse events.

Conclusions: Quetiapine demonstrated superior efficacy to placebo in patients with bipolar mania and was well tolerated.

(J Clin Psychiatry 2005;66:111–121)

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This study was supported by AstraZeneca Pharmaceuticals, Wilmington, Del.

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Bipolar disorder is a debilitating mental illness with a lifetime prevalence of approximately 3.7%.[1] The symptoms of bipolar I mania are, by definition, severe and significantly interfere with the ability to function normally.[2,3] The complexity and severity of symptoms in mania often necessitate hospitalization and call for rapid and efficacious control of symptoms. Agitation and aggression are key elements of mania and are associated with self-harm and hostility toward others. Many individuals with bipolar disorder also experience distressing psychotic symptoms.[4,5]

Pharmacologic treatment can substantially improve the symptoms of bipolar disorder. Currently recommended options include monotherapy with lithium, divalproex, carbamazepine, or an antipsychotic agent, preferably an atypical antipsychotic.[6–9] Combinations of these agents are also recommended, such as lithium or valproate plus an antipsychotic.[6–9]

Tolerability is a concern in the treatment of bipolar disorder, as many agents, particularly the conventional antipsychotics, but also traditional mood stabilizers, are associated with side effects that contribute to poor patient acceptance and adherence. Due to the favorable tolerability profile of the atypical antipsychotics, these agents are generally preferred over conventional antipsychotics.[6–9] Several atypical antipsychotics have been shown to be effective, both as combination therapy and monotherapy, in the treatment of mania in large, randomized, placebo-

controlled clinical studies.[10–18] Quetiapine fumarate is an atypical antipsychotic approved as monotherapy for the treatment of schizophrenia in most countries.[19–22] Preliminary studies[23–28] have suggested that quetiapine is effective and well tolerated in the treatment of mania associated with bipolar disorder. Quetiapine has also been shown to be effective and well tolerated in the treatment of mania when combined with lithium or divalproex in a large, randomized, placebo-controlled study in adults[29] and in combination with divalproex in a randomized, placebo-controlled study of adolescent mania and mixed mania.[30]

Here, we present the findings from a large, randomized, placebo-controlled study that was designed to evaluate the efficacy and safety of quetiapine when used as monotherapy in the treatment of mania associated with bipolar disorder.

METHOD

This multicenter, randomized, double-blind, placebo-controlled, parallel-group study was designed to compare the effects of quetiapine with placebo during a 12-week treatment period in patients initially hospitalized for a manic episode. A third group of patients was treated with lithium as an internal standard to validate assay sensitivity. The study was conducted from April 2001 to May 2002 at centers in Europe and Asia.

The study protocol was reviewed and approved by the appropriate institutional review board in accordance with the standards and guidelines established in the current amendment of the Declaration of Helsinki and was consistent with good clinical practice and applicable regulatory requirements. Written informed consent was obtained from all patients prior to any study-related activities.

Inclusion and Exclusion Criteria

Eligible subjects were adult inpatients (aged 18 years or older) hospitalized with a diagnosis of bipolar I disorder, current episode manic, according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[31] All patients had experienced at least 1 prior reliably documented manic or mixed episode. At screening and at randomization (7 days after screening), patients were required to have a score of at least 20 on the Young Mania Rating Scale (YMRS),[32] including a score of at least 4 on 2 of the 4 double-weighted YMRS items (irritability, speech, content, and disruptive/aggressive behavior). A Clinical Global Impression-Bipolar Version (CGI-BP) Severity of Illness[33] score for overall bipolar illness of at least 4 was also required. If the time from screening to randomization exceeded 7 days, screening assessments were repeated.

Patients were excluded if they had received treatment with clozapine within 28 days of the start of the study, as this population may overrepresent treatment-refractory patients. Those in a manic episode judged to be the direct physiologic consequence of a medical condition or substance use were excluded, as were patients who had been hospitalized for 3 weeks or longer for the index manic episode. Patients meeting DSM-IV criteria for rapid cycling and mixed episodes were excluded. Patients were also excluded if intolerance to quetiapine or lithium or lack of response to clozapine, quetiapine, or lithium was known to the investigator.

Use of the following medications was a criterion for excluding patients: antihypertensive agents if a stable dose had not been administered for at least 1 month before randomization; antidepressants in the week (or a period of 5 half-lives of the drug) before randomization; continuous daily use of benzodiazepines in excess of 4 mg/day of lorazepam, or the equivalent, during the month preceding screening (approximately 5 weeks prior to randomization); potent cytochrome P450 inducers, potent cytochrome P450 3A4 inhibitors, or thioridazine in the 14 days prior to randomization; and depot antipsychotic medication within 1 dosing interval prior to randomization.

Other exclusion criteria were clinically significant electrocardiogram (ECG) or laboratory results (including thyroid-stimulating hormone [TSH] concentration more than 10% above the upper limit of the normal range, regardless of treatment for hypothyroidism or hyperthyroidism), women who were pregnant or lactating, history of seizure disorder (except febrile convulsions), substance or alcohol dependence within 1 month before randomization, electroconvulsive therapy within 30 days prior to randomization, and previous participation in another clinical study or compassionate use program within 4 weeks of randomization.

Patient Population and Study Medication

On day 1, patients were randomly assigned to treatment with quetiapine or lithium or their matching placebos. All medication was administered twice daily in a double-blind fashion. Double-blinding was maintained throughout the study.

Quetiapine was flexibly dosed and initiated at target doses of 100 mg on day 1, 200 mg on day 2, 300 mg on day 3, and 400 mg on day 4. Quetiapine dose could be adjusted up to 600 mg/day on day 5 and up to 800 mg/day thereafter (days 6 to 84).

Lithium dosing was initiated on day 1 at a dose of 900 mg/day. Dose adjustment between days 5 and 84 was at the discretion of the investigator in order to optimize efficacy and tolerability. The target trough serum lithium concentration was between 0.6 and 1.4 mEq/L and was monitored throughout the study by an investigator independent of the dosing investigator. Study blinding was maintained by collecting blood samples from all patients

at least 12 hours after administration of the previous dose of study medication, and serum lithium concentrations were determined on days 4, 7, 14, 21, 28, 42, 56, 70, and 84 (or final visit). Additional tests were conducted as needed, at the discretion of the investigator, to assess lithium toxicity. In addition, all investigators and individuals who administered psychiatric rating scales remained blinded to treatment for the duration of the study.

Lithium was chosen as an active treatment standard to validate assay sensitivity. The study was prospectively powered to detect differences between quetiapine and placebo, not differences between lithium and quetiapine. However, the relative treatment effect of lithium versus quetiapine based on YMRS scores was analyzed.

After day 7, patients could be discharged to continue treatment as outpatients if the investigator believed that it was clinically appropriate.

Prior and Concomitant Medication

The exclusion criteria detail those medicines that were not allowed prior to the study. The use of any psychoactive drugs (including antidepressant, hypnotic, mood-stabilizing, anxiolytic, antipsychotic, and sedative medications other than those specifically mentioned) was not permitted from randomization to day 84. Medications were reviewed at screening and immediately prior to randomization to ensure that those not allowed by the protocol were withdrawn for a sufficient period prior to initiation of study treatment. The primary criteria were tapering any medications (over a period of approximately 1 week) known to be associated with withdrawal from treatment, e.g., antidepressants, and providing an interval of approximately 5 half-lives for the study treatments before initiation.

Medications permitted during the study included previously prescribed medications for stable medical, nonpsychiatric illnesses; oral contraceptives and contraceptive devices; and antihypertensive treatments, providing the dosage had remained stable for at least 1 month prior to randomization. The following sedatives/hypnotics were permitted during the study for insomnia, providing the maximum doses were not exceeded and only 1 was used on any study day: zolpidem tartrate (maximum dose = 10 mg/day), chloral hydrate (maximum dose = 2 g/day from days 1 to 7 and 1 g/day from days 8 to 84), zopiclone (maximum dose = 7.5 mg/day), and zaleplon (maximum dose = 20 mg/day). Use of concomitant anticholinergic medications was not allowed after randomization unless in relation to an adverse event of extrapyramidal symptoms (EPS).

Lorazepam treatment for agitation (but not insomnia) was allowed as follows: up to 6 mg/day from screening to day 4, up to 4 mg/day from days 5 to 7, up to 2 mg/day from days 8 to 10, and up to 1 mg/day from days 11 to 14. Lorazepam was withheld for 6 hours before psychiatric assessments were conducted and was not permitted by the protocol after day 14. Within these guidelines, treatment was at the discretion of the physician, and if a patient experienced insomnia and agitation concurrently, lorazepam plus one of the permitted sedatives/hypnotics could be coadministered.

Efficacy Evaluations

Severity of illness and psychopathology were measured using the YMRS,[32] the Positive and Negative Syndrome Scale (PANSS),[34] and the Montgomery-Asberg Depression Rating Scale (MADRS).[35] The Clinical Global Impressions (CGI)[36] and CGI-BP[33] scales were used to confirm the clinical relevance of changes in the efficacy assessment scales. In addition, patient functioning was assessed with the Global Assessment Scale (GAS).[37]

Efficacy assessments, with the exception of GAS, were conducted on days 1 (baseline), 4, 7, 14, 21, 28, 42, 56, 70, and 84. GAS assessments were made on days 1, 21, and 84.

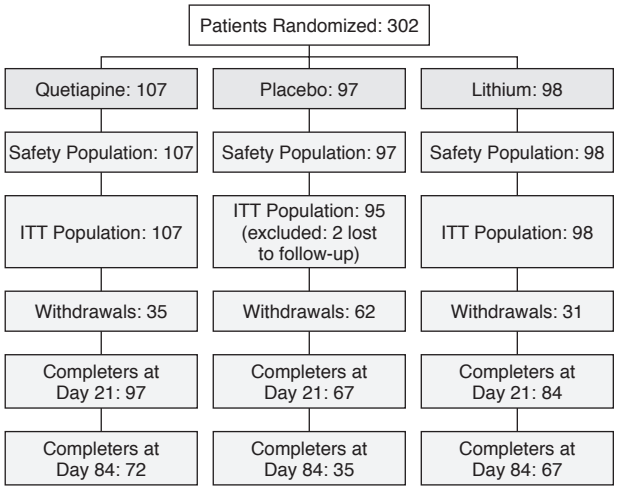
The primary efficacy endpoint was the change from baseline in YMRS score at day 21. Secondary endpoints (assessed at days 21 and 84, unless otherwise specified) were change from baseline in YMRS score at day 84, YMRS response rate (defined as a $\geq 50\%$ decrease in YMRS score from baseline), and YMRS remission rate (defined as a YMRS score of ≤ 12). In addition, the proportion of patients who maintained their day 21 YMRS response or remission at day 84 was evaluated.

Other secondary endpoints at days 21 and 84 were Severity of Illness score change from baseline and Global Improvement scores for both the CGI-BP and CGI; change from baseline in PANSS total and PANSS positive, activation, and supplemental aggression risk subscale scores; change from baseline in MADRS score; percentage of patients using lorazepam; percentage of patients using sedatives/hypnotics; and change from baseline in GAS scores.

Safety Evaluations

Vital sign measurements were performed at baseline (day 1) and at days 4, 7, 14, 21, 28, 42, 56, 70, and 84 (final visit). Patients were examined and questioned on all study days regarding any adverse events. Safety evaluations were based on reports of adverse events, trough serum concentrations, concomitant medication records, vital signs, weight, and clinical laboratory parameters (including prolactin, nonfasting/random glucose, electrolyte, and thyroid levels and hematologic analysis). Adverse events included any treatment-emergent symptoms or worsening of existing symptoms, new illnesses, or clinically significant changes in laboratory tests, vital signs, weight, or ECG results. Treatment-emergent depression, defined a priori as a MADRS score ≥ 18 and an increase of ≥ 4 from baseline on any 2 consecutive postbaseline

Figure 1. Study Profile (ITT population)



Abbreviation: ITT = intent-to-treat.

Table 1. Summary of Baseline Demographic Data and Disease Characteristics (ITT population)

Characteristic	Quetiapine (N = 107)	Placebo (N = 95)	Lithium (N = 98)
Gender, N (%)			
Male	60 (56.1)	55 (57.9)	58 (59.2)
Female	47 (43.9)	40 (42.1)	40 (40.8)
Age, y			
Mean	38.0	41.3	38.8
Range	18–72	18–70	18–73
Weight, kg			
Mean	65.1	63.4	63.1
Range	37–119	36–100	33–102
BMI, mean, kg/m^2	23.8	23.1	23.2
YMRS score, mean	32.7	34.0	33.3
MADRS score, mean	6.1	6.2	6.3
PANSS score, mean	58.2	58.7	58.0
CGI-BP Severity of Illness score, mean	4.9	5.0	4.9
Bipolar I disorder, most recent episode, N (%)			
Manic moderate	37 (34.6)	26 (27.4)	30 (30.6)
Manic severe without psychotic features	42 (39.3)	37 (38.9)	45 (45.9)
Manic severe with psychotic features	28 (26.2)	32 (33.7)	23 (23.5)

Abbreviations: BMI = body mass index, CGI-BP = Clinical Global Impression-Bipolar Version, ITT = intent-to-treat, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, YMRS = Young Mania Rating Scale.

visits, or at the final study visit, was also monitored. EPS were assessed with adverse event reporting, the Simpson-Angus Scale (SAS),[38] and the Barnes Akathisia Rating Scale (BARS).[39]

Statistical Analysis

The primary and secondary efficacy analyses were performed on the intent-to-treat (ITT) population, which included all randomized patients who took at least 1 dose of study medication and who had baseline and at least 1 set of postbaseline YMRS assessments. A last-observation-carried-forward (LOCF) approach was used in the primary assessment of each of the efficacy endpoints.

The primary and secondary efficacy outcome variables measured by rating scales were analyzed using analysis of covariance models. Adjustments were made for the baseline value by including the baseline as a covariate in the primary model.

When comparing quetiapine with placebo for binary response variables, the Cochran-Mantel-Haenszel test was used.

All statistical tests were 2-tailed, with a significance level of .05.

RESULTS

Patient Demographics and Disposition

A total of 302 patients were randomly allocated to receive quetiapine (N = 107), placebo (N = 97), or lithium (N = 98) (Figure 1). The ITT population comprised 107 patients in the quetiapine group, 95 in the placebo group, and 98 in the lithium group.

The demographics of the treatment groups were generally similar at baseline (Table 1). Disease characteristics were similar in terms of YMRS scores for all patient groups (Table 1).

More patients treated with quetiapine (67.3%) or lithium (68.4%) completed the study at day 84 compared with those treated with placebo (36.1%). The main reasons for discontinuation in the placebo group were deterioration of disease and lack of efficacy (Table 2).

Quetiapine and Lithium Dose

At day 21, 90% of patients who responded to quetiapine were taking doses between 400 and 800 mg/day. At day 84, 91% of responders were taking doses in this range. The mean quetiapine dose for responders was 586 mg/day in the last week of treatment prior to day 21 and 618 mg/day prior to day 84 (mean doses calculated by averaging the median dose for responders in the last week of treatment). The mean serum lithium concentrations in lithium-treated patients were within the target range of 0.6 to 1.4 mEq/L at all assessments from day 4 onward. The median serum lithium concentration was 0.73 mEq/L at day 14, 0.80 mEq/L at day 21, and 0.80 mEq/L at day 84.

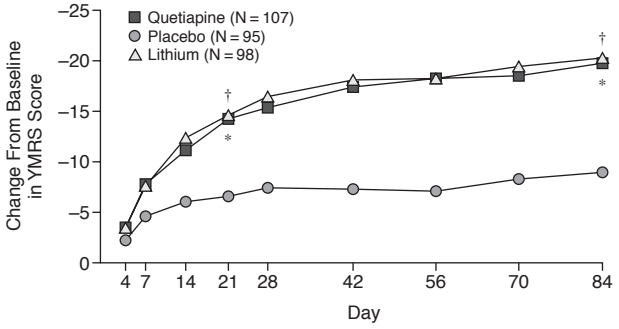
Concomitant Medications

Approximately 71% of patients had taken at least 1 antipsychotic medication (mainly typical antipsychotics) in the 28 days prior to randomization. The number of days of use of typical antipsychotics was similar in all treatment groups (a median of 7 to 8 days across all groups).

Table 2. Patient Disposition and Withdrawals, N (%)

Disposition	Quetiapine (N = 107)	Placebo (N = 97)	Lithium (N = 98)
Withdrawals	35 (32.7)	62 (63.9)	31 (31.6)
Lack of efficacy/disease deterioration	16 (14.9)	38 (39.2)	12 (12.2)
Lost to follow-up	2 (1.9)	4 (4.1)	1 (1.0)
Adverse events or concurrent illness	7 (6.5)	4 (4.1)	6 (6.1)
Protocol nonadherence	2 (1.9)	1 (1.0)	2 (2.0)
Informed consent withdrawn	7 (6.5)	13 (13.4)	10 (10.2)
Other	1 (0.9)	2 (2.1)	0
Completers at day 21	97 (90.7)	67 (69.1)	84 (85.7)
Completers at day 84	72 (67.3)	35 (36.1)	67 (68.4)

Figure 2. Change From Baseline in YMRS Scores Over Time (LOCF, ITT population)[a]



[a]Values are least squares mean.
*Quetiapine versus placebo, p < .001.
†Lithium versus placebo, p < .001.
Abbreviations: ITT = intent-to-treat, LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

The majority of patients had used no mood-stabilizing medication in the 28 days prior to randomization, and in general there were no differences between treatment groups. Of the patients who had received a mood-stabilizing drug, the majority had taken lithium. Overall, 15% of the patients in the ITT population used lithium in the 28 days preceding randomization: 17% of quetiapine-treated patients, 12% of placebo-treated patients, and 17% of lithium-treated patients. Five percent of patients in the ITT population had taken valproate (5% of quetiapine-treated patients, 4% of placebo-treated patients, and 5% of lithium-treated patients), and 6% had taken carbamazepine, lamotrigine, or topiramate (6% of quetiapine-treated patients, 8% of placebo-treated patients, and 5% of lithium-treated patients).

Lorazepam use in the first 14 days of the study was numerically higher in the placebo-treated group than in the quetiapine-treated or lithium-treated groups (46.3%, 36.1%, and 31.2%, respectively). In all groups, the proportion of patients who used lorazepam decreased over time. A small number of patients used lorazepam after day 14 (4 quetiapine-treated patients, 11 placebo-treated patients, and 9 lithium-treated patients), although this was prohibited by the protocol.

On days 15 to 21, the percentage of patients who used sleep medications at least once was 25.5% in the quetiapine group, 42.0% in the placebo group, and 30.0% in the lithium group. Sleep medication use declined over the course of the study in all groups. Over the course of the whole study, the percentage of patients who used sleep medications at least once was numerically lower in the quetiapine group (47.7%) compared with the placebo (58.8%) and lithium groups (56.1%). Use of anticholinergic medications was low in all groups (11.2% of quetiapine patients, 8.3% of placebo patients, and 12.2% of lithium patients) and consistent with the low incidence of EPS.

Efficacy

Primary endpoint. There was a statistically significant difference in change from baseline in YMRS score between the quetiapine- and placebo-treated groups from day 7 onward (–8.03 versus –4.89; p < .01) (Figure 2). The advantage of quetiapine over placebo continued to increase with treatment duration. At the primary endpoint (day 21), the difference between the groups was larger (–14.62 versus –6.71; p < .001) than at day 7 and continued to increase until the end of the study (day 84), when the difference was still significant (–20.28 versus –9.00; p < .001).

YMRS scores for the lithium-treated patients were significantly improved compared with those for the placebo group at day 7 (–7.24 versus –4.89; p < .05), day 21 (–15.20 versus –6.71; p < .001), and day 84 (–20.76 versus –9.00; p < .001).

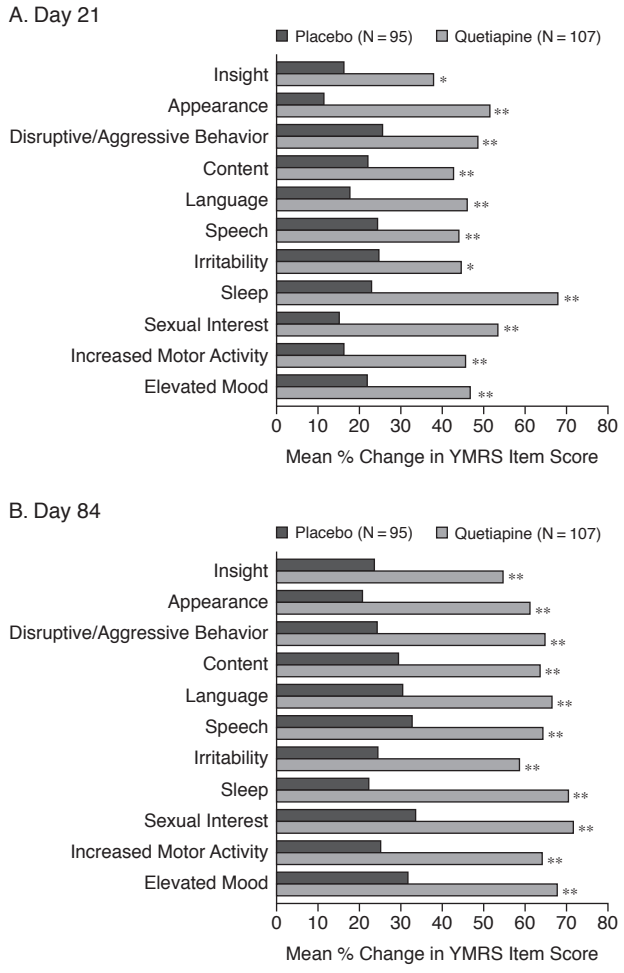
A comparison of the 2 active treatments relative to each other at days 21 and 84 showed similar improvements in YMRS scores with quetiapine and lithium monotherapy at both days. There was no statistically significant difference between the 2 treatments.

Individual YMRS items. Scores on all 11 items on the YMRS were significantly improved with quetiapine treatment compared with placebo at day 21 and onward (Figure 3).

Secondary endpoints

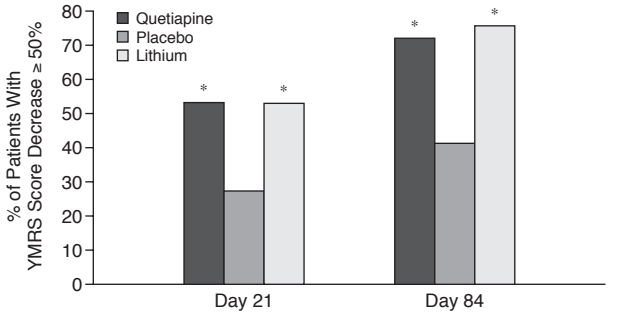
Response rates. The YMRS response rate (a 50% or greater reduction in YMRS score from baseline) at day 21 was significantly greater for quetiapine-treated patients than for those receiving placebo (53.3% versus 27.4%; p < .001) (Figure 4). This significant difference between quetiapine and placebo was maintained at day 84 (72.0% versus 41.1%; p < .001) (Figure 4). Most patients who were responders to quetiapine at day 21 maintained their response at day 84 (88%). Of individuals nonresponsive at day 21 who had a further assessment, 68.4% of quetiapine-treated patients had responded by day 84,

Figure 3. Percent Change in YMRS Item Scores at Days 21 (A) and 84 (B) (LOCF, ITT population)



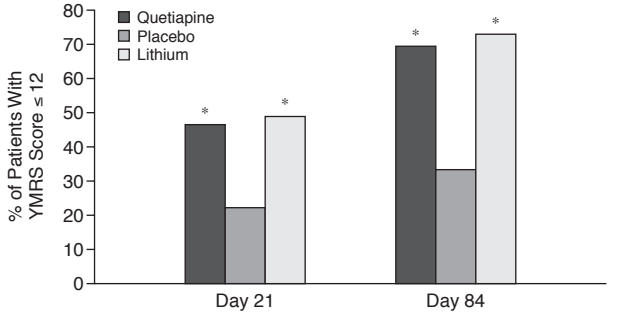
*p < .01.
**p < .001 versus placebo.
Abbreviations: ITT = intent-to-treat, LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

Figure 4. YMRS Response Rates at Days 21 and 84 (LOCF, ITT population)



*p < .001 versus placebo.
Abbreviations: ITT = intent-to-treat, LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

Figure 5. YMRS Remission Rates at Days 21 and 84 (LOCF, ITT population)



*p < .001 versus placebo.
Abbreviations: ITT = intent-to-treat, LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

compared with 41.0% of placebo-treated patients. For the lithium group, the YMRS response rates at days 21 (53.1%; p < .001) and 84 (75.5%; p < .001) were also significantly greater than for the placebo group (Figure 4).

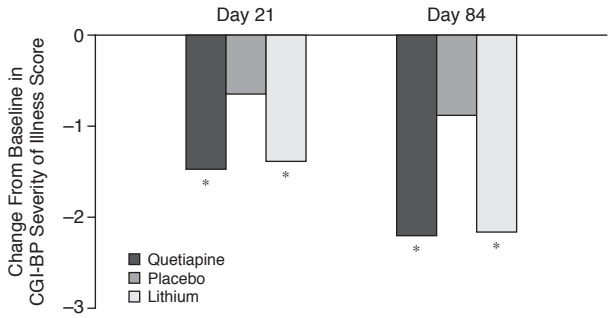
Remission rates. The proportion of patients experiencing YMRS remission (YMRS score ≤ 12) at day 21 with quetiapine treatment was significantly greater than with placebo (46.7% versus 22.1%; p < .001) and increased by day 84 (69.2% versus 33.7%; p < .001) (Figure 5). Similarly, in the lithium-treated patients, the YMRS remission rates at day 21 (49.0%; p < .001) and day 84 (72.4%; p < .001) were significantly greater than in the placebo group (Figure 5).

Clinical Global Impression-Bipolar Version. At day 21, a statistically significant difference was seen in the change from baseline in CGI-BP Severity of Illness score between the quetiapine and placebo treatment groups (–1.48 versus –0.66; p < .001) (Figure 6). At day 84, the difference between quetiapine and placebo was greater (–2.20 versus –0.89; p < .001).

In the lithium group, there was also a significant difference from placebo in change from baseline in CGI-BP Severity of Illness score at days 21 (–1.41 versus –0.66; p < .001) and 84 (–2.18 versus –0.89; p < .001) (Figure 6).

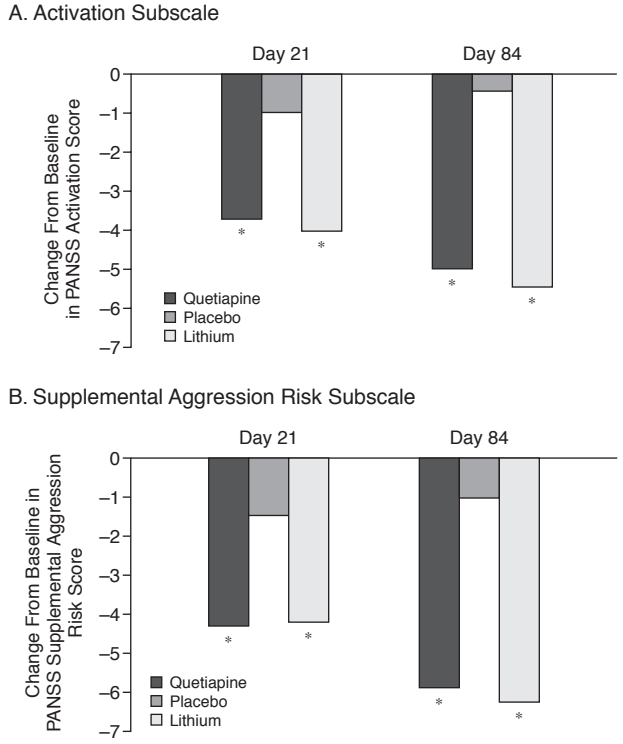
The percentage of patients who were rated as "much" or "very much" improved from baseline on the CGI-BP Global Improvement score was significantly greater in the quetiapine group compared with the placebo group at day 21 (63.6% versus 30.5%; p < .001). Similarly, a significant difference between the quetiapine and placebo groups was seen at day 84 (72.0% versus 36.8%; p < .001). The lithium-treated group also showed a statistically significant advantage over the placebo group at day 21 (64.3% versus 30.5%; p < .001) and day 84 (72.4% versus 36.8%; p < .001).

Figure 6. Reduction in CGI-BP Severity of Illness Scores From Baseline at Days 21 and 84 (LOCF, ITT population)



*p < .001 versus placebo.
Abbreviations: CGI-BP = Clinical Global Impression-Bipolar Version, ITT = intent-to-treat, LOCF = last observation carried forward.

Figure 7. PANSS Activation (A) and Supplemental Aggression Risk (B) Subscale Scores at Days 21 and 84 (LOCF, ITT population)



*p < .001 versus placebo.
Abbreviations: ITT = intent-to-treat, LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

For the CGI Global Improvement score and change from baseline in CGI Severity of Illness score at days 21 and 84, there were statistically significant differences between quetiapine and placebo and between lithium and placebo of similar magnitude (data not shown) to those reported for the CGI-BP endpoints.

Positive and Negative Syndrome Scale. The total scores on the PANSS were similar at baseline for quetiapine, placebo, and lithium (Table 1). At day 21, quetiapine treatment resulted in a statistically significant reduction compared with placebo in PANSS total score (–8.71 versus –2.12; $p < .001$) and PANSS positive subscale score (–4.93 versus –1.55; $p < .001$). At day 84, similar significant reductions were seen with quetiapine compared with placebo for total (–11.78 versus –1.04; $p < .001$) and positive subscale scores (–6.85 versus –1.48; $p < .001$). Similar statistically significant effects were seen with lithium treatment compared with placebo.

The reduction in the PANSS activation subscale score at day 21 was significantly greater in quetiapine-treated patients compared with placebo-treated patients (–3.69 versus –1.0; $p < .001$) (Figure 7). The difference in the treatment groups increased with time, with a significant reduction also observed with quetiapine treatment at day 84 (–4.97 versus –0.49; $p < .001$) (Figure 7). PANSS supplemental aggression risk subscale scores were similar at baseline in the quetiapine- and placebo-treated patients. At day 21, the quetiapine group had significantly reduced scores compared with the placebo group (–4.29 versus –1.50; $p < .001$). The difference in the aggression risk scores between the quetiapine and placebo groups increased at day 84 (–5.87 versus –1.07; $p < .001$). Treatment with lithium also resulted in a significantly greater reduction in the PANSS total score and the PANSS activation and supplemental aggression risk subscale scores compared with placebo ($p < .001$ in all cases).

Montgomery-Asberg Depression Rating Scale. Baseline MADRS scores were low and similar for the quetiapine, placebo, and lithium groups (Table 1). At day 21, the change from baseline with quetiapine treatment was significantly different from placebo (–1.55 versus –0.05; $p = .015$). Continued improvement in MADRS scores was noted with treatment duration, and at day 84 the change from baseline in MADRS scores for quetiapine compared with placebo remained significantly different (–1.49 versus +1.21; $p = .002$). Lithium treatment significantly reduced the MADRS score compared with placebo only at day 84 (–1.83 versus +1.21; $p = .001$).

Global Assessment Scale. Patients in the quetiapine group had a significant improvement from baseline in GAS score compared with placebo at day 21 (17.96 versus 5.59; $p < .001$) and day 84 (26.35 versus 9.26; $p < .001$). Similar improvements were seen with lithium treatment compared with placebo at days 21 and 84.

Safety

Most adverse events were mild or moderate. Withdrawal rates due to adverse events or concurrent illness were 6.5% in the quetiapine group, 4.1% in the placebo

Table 3. Adverse Events Occurring at an Incidence of ≥ 5% in Quetiapine or Lithium Groups, N (%)

Adverse Event[a]	Quetiapine (N = 107)	Placebo (N = 97)	Lithium (N = 98)
Dry mouth	26 (24.3)	2 (2.1)	6 (6.1)
Somnolence	21 (19.6)	3 (3.1)	9 (9.2)
Weight gain	16 (15.0)	1 (1.0)	6 (6.1)
Dizziness	13 (12.1)	2 (2.1)	7 (7.1)
Insomnia	10 (9.3)	20 (20.6)	16 (16.3)
Headache	8 (7.5)	4 (4.1)	12 (12.2)
Asthenia	7 (6.5)	1 (1.0)	4 (4.1)
Depression	6 (5.6)	1 (1.0)	1 (1.0)
Tremor	6 (5.6)	4 (4.1)	18 (18.4)
Diarrhea	5 (4.7)	4 (4.1)	5 (5.1)
Weight loss	2 (1.9)	1 (1.0)	6 (6.1)
Anorexia	1 (0.9)	4 (4.1)	9 (9.2)
Nausea	1 (0.9)	2 (2.1)	6 (6.1)
Vomiting	1 (0.9)	2 (2.1)	6 (6.1)

[a]Patients with multiple events falling under the same event term are counted only once in that term.

group, and 6.1% in the lithium group. Adverse events occurring in ≥ 10% of patients were dry mouth (24.3%), somnolence (19.6%), weight gain (15.0%), and dizziness (12.1%) in the quetiapine group; insomnia (20.6%) in the placebo group; and tremor (18.4%), insomnia (16.3%), and headache (12.2%) in the lithium group (Table 3).

There were no significant differences in change from baseline in total SAS and BARS scores between the quetiapine and placebo groups, consistent with the low rate of EPS-related adverse events (13.1% versus 9.3%) in these groups. A smaller proportion of patients in the quetiapine-treated group experienced akathisia (0.9%) compared with the placebo-treated (6.1%) and lithium-treated (3.1%) groups. Lithium was associated with a higher incidence of tremor than quetiapine or placebo (Table 3). Overall, the incidence of EPS (including akathisia) in the quetiapine group did not differ from that in the placebo group.

The mean weight gain in the quetiapine group was significantly ($p < .001$) higher than that in the placebo group: 2.6 versus –0.08 kg (LOCF) and 3.3 versus 0.3 kg (observed cases). Weight gain ≥ 7% from baseline at day 84, adjusted for baseline body mass index (BMI) category, was also significantly more frequent in the quetiapine group than in the placebo group ($p = .008$). Most patients who gained ≥ 7% of their weight belonged to the group with baseline BMI < 25 (underweight or normal weight) (placebo: 9.2%, quetiapine: 33.3%, and lithium: 16.9%), while a smaller proportion belonged to the group with baseline BMI ≥ 25 (overweight, obese, or severely obese) (placebo: 6.3%, quetiapine: 24.4%, and lithium: 12.1%). These data suggest that significant weight gain was mitigated by its relatively greater incidence in patients with lower baseline weight. In the lithium group, the mean weight gain of 0.7 kg (LOCF) and 1.0 kg (observed cases) was not significantly different from placebo. There were no discontinuations due to weight gain in any group.

The placebo-treated group had the highest proportion of patients with protocol-defined emergent depression at day 84 (8.4%, 5.6%, and 3.1% for placebo, quetiapine, and lithium, respectively), but the difference between active treatments and placebo was not statistically significant.

While the mean prolactin concentration was high at baseline (32.7 to 35.6 μg/L) in all 3 groups, it had decreased substantially by day 84: –18.4 μg/L in the quetiapine group, –13.2 μg/L in the placebo group, and –17.3 μg/L in the lithium group. The proportion of patients with a shift to potentially significant high levels of prolactin (> 20 μg/L in men, > 30 μg/L in women) was 6/53 (11.3%) in the quetiapine group, 6/47 (12.8%) in the placebo group, and 7/55 (12.7%) in the lithium group.

The proportion of lithium-treated patients with clinically significant increases in TSH concentration was 15.7% (14/89), compared with 1.0% (1/97) in the quetiapine-treated group and 1.1% (1/87) in the placebo-treated group. None of these patients had a potentially clinically significant free or total thyroxine concentration, and there were no adverse events of clinical hypothyroidism.

There were no clinically important differences among the treatment groups with respect to vital signs (including orthostatic changes), ECGs, hematology, or clinical chemistry parameters (including changes in glucose concentrations).

DISCUSSION

The results of this study indicate that quetiapine is effective and well tolerated for the short-term and continuation phase treatment of patients with bipolar mania.

Quetiapine was statistically superior to placebo at day 7 of treatment and at the primary endpoint (day 21), with continued significant improvement observed to day 84. Improvement in mania was distributed broadly across the individual items of the YMRS, and quetiapine significantly improved each of the 4 core double-weighted YMRS items[32] by day 21.

All secondary endpoints for quetiapine were statistically superior to placebo at days 21 and 84, including psychotic symptoms, agitation, and aggression, and these improvements were independent of the presence of psychotic symptoms at baseline (DSM-IV diagnosis).

Few studies have reported 12-week, double-blind, placebo-controlled data for the treatment of mania with which to compare these findings. This is the first such study of lithium for this duration and only the third trial of lithium in mania with a parallel-group, placebo-controlled design.[40,41] The magnitude of improvement over placebo with quetiapine by the 3-week endpoint in this study is similar to that reported for divalproex, lithium, and other atypical antipsychotics.[10–18,40]

A greater proportion of patients responded to quetiapine compared with placebo at all time points. Moreover,

87.7% of patients who achieved 50% or greater improvement in YMRS score compared with baseline in response to quetiapine maintained the response over the 3-month study period. Of the small proportion of patients who did not respond to quetiapine by day 21, more than half of these (68.4%) converted to responders by day 84.

A significantly higher proportion of patients treated with quetiapine in this study achieved clinical remission compared with placebo at day 21 and day 84. These clinical remission rates, defined as a YMRS score of 12 or less,[11] help to confirm the clinical relevance of the other improvements observed.

Further evidence of clinically relevant improvement with quetiapine treatment was observed in significant improvements on the CGI-BP Global Improvement scale. These findings indicate that the improvement in mania was not associated with important clinical adverse effects or a worsening of the other symptoms of bipolar disorder (e.g., depression).

These results add to the evidence from 2 other randomized, parallel-group studies of lithium indicating that the drug is efficacious in well-designed studies and comparable in efficacy to drugs such as quetiapine.[40,41] These studies also indicate the adverse effects of lithium that constrain both its acute and its long-term use, particularly given the growing number of alternative treatments for mania.[42]

In our study, quetiapine significantly improved mania-associated agitation and aggression compared with placebo, as measured by the PANSS activation and supplemental aggression risk subscales. This finding has clinical relevance, since agitation and aggression, in the form of violence toward self, family members, and health care personnel, contribute substantially to the morbidity and mortality that can occur in mania.

The change from baseline in MADRS scores and the proportion of patients meeting an a priori definition of emergent depression were determined to monitor any possible treatment-related worsening of depression. The rate of emergent depression was low and similar in the placebo and quetiapine groups. Despite low MADRS scores at baseline, quetiapine treatment resulted in improved MADRS scores at day 21 that were significantly different from placebo by the end of the study (day 84). The results suggest that quetiapine may improve depressive symptoms in patients with mania.

The design of this study included assessments up to 12 weeks to determine improvement in effect, maintenance of effect, and the safety profile over a longer time period. The 12-week study duration was important with regard to treatment-related depression, as symptoms may take longer than 3 weeks to emerge. It was encouraging, therefore, that quetiapine was not associated with treatment-emergent depression over the 12-week double-blind assessment period, indicating that quetiapine does not induce or worsen depression in patients with mania.

Taken together, the above findings indicate that quetiapine is effective in the treatment of a broad range of symptoms in patients with mania associated with bipolar disorder.

Since this study utilized a flexible dosing design, conventional dose-response analyses are not possible. However, the average dose in responders can provide an estimate of the therapeutic dose range of quetiapine. In the majority of patients, the effective dose of quetiapine was within the range of 400 to 800 mg/day, with a mean dose of approximately 600 mg/day in responders at days 21 and 84 (calculated by averaging the median dose for responders in the last week of treatment). The simple and rapid quetiapine dosing regimen used in this study was generally well tolerated across the entire dose range.

Some randomized, controlled studies of atypical antipsychotics in acute bipolar mania allowed the use of lorazepam but did not permit concurrent sleep medications.[10,11] The present study, as well as those by Keck et al.[14] and Sachs et al.,[18] did allow a medication for insomnia. However, the use of both lorazepam and sleep medication was lower in the quetiapine group than in the placebo or lithium groups in this study.

The overall rate of adverse events leading to withdrawal with quetiapine was low and similar to that observed with placebo. A greater proportion of patients in the placebo group withdrew from therapy, mainly due to deterioration in the course of the disease or a lack of efficacy. The most frequently reported adverse events for the quetiapine-treated group were dry mouth and somnolence. Somnolence was more common in quetiapine-treated patients, but was consistently mild and transient, occurred with greater frequency in the first few days, and was not a reason for discontinuation for any patient. The effects of somnolence may be beneficial during the acute treatment of patients with mania, who are often agitated and experience difficulty sleeping. However, the efficacy of quetiapine appeared to be independent of somnolence, as response rates were similar in patients who reported somnolence compared with those who did not. Insomnia, often seen in patients with mania, was more common in patients treated with placebo.

Since treatment for bipolar disorder is usually long-term, treatment-associated weight gain is an important issue. Most currently available agents, such as olanzapine,[10,11] lithium, and divalproex, are associated with some weight gain. In the current study, weight gain with quetiapine was principally observed among patients with initial BMIs below 25 and may, therefore, be less problematic among obese individuals.

Typical antipsychotics and several atypical antipsychotics are associated with a high risk of EPS, which generally lead to treatment discontinuation.[43] In this 12-week

study, EPS (including akathisia) in quetiapine-treated patients were no different than in the placebo group. Most adverse events of tremor occurred in the lithium-treated group, which is likely to be a reflection of the known effects of lithium in causing tremor.

All 3 treatment groups had elevated baseline prolactin levels in this study, probably related to the widespread use of typical antipsychotics prior to study entry. Prolactin levels decreased significantly in all groups by the end of the study, indicating that quetiapine had placebo-like effects on prolactin in this 12-week study. As changes in weight, EPS, or prolactin level can have long-term consequences, further information on the benefits of quetiapine with regard to these parameters in longer-term studies would be of interest.

Increase in TSH concentration, an index of reduced thyroid function, as a side effect of lithium treatment is consistent with observations in the present study, as the highest proportion of patients with a clinically significant increase in TSH concentration occurred in the lithium group. Mean decreases in free and total thyroxine were observed in the quetiapine group, without clinically significant increases in TSH concentration. These changes in thyroxine are consistent with the known safety profile of quetiapine.

Patients with mania associated with bipolar disorder have impaired functioning, as work, social, and/or other aspects of life are usually affected. It is therefore important that a treatment for mania improve both symptoms and overall functioning in these patients. As evidenced by the improvement in GAS scores over the 12-week treatment period, quetiapine monotherapy resulted in continued improvement in functioning, which correlated with symptomatic recovery.

In conclusion, this study provides evidence for the efficacy of quetiapine as monotherapy for the treatment of mania in patients with bipolar disorder. Quetiapine was well tolerated, with a safety profile similar to that seen in studies of schizophrenia, particularly the low, placebo-level incidence of both EPS (including akathisia) and serum prolactin elevation.[19–22] These findings are consistent with several other studies that have found quetiapine to be effective and well tolerated in the treatment of bipolar mania.[24–30,44] The efficacy and tolerability of quetiapine reported in this study support the conclusion that it is a clinically effective treatment for bipolar mania up to 3 months. Further long-term studies are warranted.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril, Fazaclo, and others), divalproex (Depakote), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), topiramate (Topamax), zaleplon (Sonata), zolpidem (Ambien).

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