Efficacy and Safety of Quetiapine in Children and Adolescents With Mania Associated With Bipolar I Disorder: A 3-Week, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Objective: To evaluate the efficacy and safety of quetiapine monotherapy in children and adolescents with mania associated with bipolar I disorder.

Method: Patients aged 10 to 17 years, with a *DSM-IV-TR* diagnosis of a manic episode associated with bipolar I disorder and Young Mania Rating Scale (YMRS) total score ≥ 20 were randomized to 3 weeks of quetiapine (400 or 600 mg/d) or placebo. The primary efficacy measure was change in YMRS total score. The study was conducted at 34 centers in the United States between August 2004 and July 2006.

Results: The intent-to-treat population included 277 patients. Least squares mean change in YMRS score from baseline to end point by mixed-model, repeated-measures analysis was –14.25, –15.60, and –9.04 for quetiapine 400 mg/d, quetiapine 600 mg/d, and placebo, respectively ($P < .001$, each quetiapine dose vs placebo). Significant improvement in YMRS score versus placebo was first observed at day 4 ($P = .015$) with quetiapine 400 mg/d and day 7 ($P < .001$) with quetiapine 600 mg/d. Mean changes in body weight at day 21 (observed cases) were 1.7 kg for both quetiapine doses and 0.4 kg for placebo. Numerically larger mean increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides were observed with quetiapine than placebo. Adverse events associated with quetiapine were mostly mild to moderate in intensity.

Conclusions: In this 3-week study, quetiapine was significantly more effective than placebo in improving manic symptoms in youth with mania associated with bipolar disorder. Treatment was generally well tolerated and adverse events were broadly consistent with the known profile of quetiapine in adults with bipolar disorder.

Trial Registration: ClinicalTrials.gov identifier: NCT00090311

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Early recognition and prompt initiation of effective treatment are key management goals in youth with bipolar disorder.[1–6] Whereas numerous medications are available to treat adults with bipolar disorder, study data to support the efficacy of medications in children and adolescents are comparatively limited.[7–9] Emerging evidence indicates that the atypical antipsychotics, which are used with increasing frequency in adults,[10] also have efficacy for the acute treatment of bipolar disorder in youth.[11–15]

Quetiapine is an atypical antipsychotic approved by the US Food and Drug Administration (FDA) for treating adults with schizophrenia, acute manic episodes associated with bipolar I disorder, depressive episodes associated with bipolar disorder, and as maintenance treatment of bipolar I disorder (adjunctive to lithium or divalproex). Quetiapine extended-release is also approved as adjunctive treatment of major depressive disorder.

Quetiapine has been investigated in controlled studies of adolescents with manic or depressive symptoms of bipolar disorder.[16–19] In acute (4- and 6-week) studies of adolescents with bipolar mania, quetiapine (400–600 mg/d) was as effective as divalproex for alleviating manic symptoms, while quetiapine (450 mg/d) combined with divalproex was more effective than divalproex alone.

The current 3-week, placebo-controlled trial (ClinicalTrials.gov identifier: NCT00090311) evaluated quetiapine at fixed doses of 400 mg/d or 600 mg/d for the acute treatment of youth with bipolar I disorder with manic episodes. The results of this trial served, in part, as a basis for the FDA's approval of quetiapine for treating acute manic episodes of bipolar disorder in children and adolescents aged 10 to 17 years.

METHOD

Study Design

This double-blind, randomized, placebo-controlled, parallel-group study of quetiapine in youth was conducted at 34 centers in the United States between August 2004 and July 2006.

The study was approved by institutional review boards at each site and performed in accordance with the current amendment of the Declaration of Helsinki and International Conference on Harmonization/Good Clinical Practice Guidelines. The parents or legal guardians of all patients provided written, informed consent and all patients provided written assent. Patients could withdraw from the study at any time if they or their parent/guardian no longer wished to participate or at the investigators' discretion.

Patient Population

Boys and girls aged 10 to 17 years, inpatients or outpatients, with a diagnosis of bipolar I disorder with manic episodes defined by the *Diagnostic and Statistical Manual for Mental Disorders,* Fourth Edition, Text Revision[20] were eligible for study inclusion. Diagnoses were confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version.[21] Patients were required to have a Young Mania Rating Scale (YMRS)[22] total score ≥ 20 at screening and

Clinical Points

- This article describes the first large, randomized, placebo-controlled study of the efficacy and safety of quetiapine monotherapy in youth with bipolar I disorder with manic episodes.
- Quetiapine for 3 weeks at fixed doses of 400 or 600 mg/d was associated with significantly greater improvements in YMRS total score (the primary efficacy measure) compared with placebo, with a rapid onset of effect.
- Adverse events associated with quetiapine were consistent with its profile in adults with bipolar disorder. The most common adverse events in quetiapine-treated patients included somnolence, sedation, dizziness, and headache.
- The large population size studied and the broad range of efficacy and safety measures that were investigated support a role for this study in informing clinical practice.

randomization (ie, baseline) and were permitted to have a secondary diagnosis of attention-deficit/hyperactivity disorder (ADHD). Trained clinicians (child psychiatrists or psychologists) administered diagnostic and rating scales.

Exclusion criteria included a current *DSM-IV*–diagnosed Axis I disorder other than bipolar I disorder or ADHD, a history of serious suicide attempts, or a current risk for suicide or homicide in the judgment of investigators. Other exclusion criteria are included in Supplementary eTable 1 (available at PSYCHIATRIST.COM).

A screening phase included washout of previous psychoactive medications, including quetiapine, for a duration of up to 28 days that was dependent on the medications involved and at the discretion of the investigator. Patients were randomly assigned in 1:1:1 ratio to receive quetiapine 400 mg/d, quetiapine 600 mg/d, or placebo for 3 weeks. Randomization was achieved by a central randomization service, with stratification by age (10–12 years or 13–17 years).

Study Medication

The 2 quetiapine doses investigated (400 mg/d and 600 mg/d) were selected on the basis of experience from quetiapine studies in adults with bipolar mania.[23,24] The quetiapine dose was titrated from 50 mg/d on day 1 to 100 mg/d on day 2 and increased by 100 mg each day to 400 mg/d by day 5 or 600 mg/d by day 7. Quetiapine or placebo was administered orally twice daily, with an option for 3 administrations per day at the discretion of investigators, based on tolerability. Quetiapine and placebo tablets were identical in size and color to maintain blinding.

Concomitant Medication

Patients were permitted to continue psychostimulant use at stable doses for comorbid ADHD. Diphenhydramine for sleeplessness, hydroxyzine or lorazepam for agitation or anxiety, and benztropine for treatment-emergent extrapyramidal symptoms were permitted, while prophylactic use of benztropine was prohibited.

Efficacy Evaluations

The primary efficacy evaluation was mean change from baseline to day 21 (end point) in YMRS total score. Secondary efficacy measures included proportions of patients achieving criteria for response (ie, ≥ 50% reduction in YMRS score) and remission (YMRS score ≤ 12) at day 21. Changes in Children's Depression Rating Scale-Revised (CDRS-R),[25] Clinical Global Impressions-Bipolar Version (CGI-BP) Severity of Illness,[26] CGI-BP-Global Improvement score and response rate, Children's Global Assessment Scale (CGAS),[27] and Overt Aggression Scale-Modified scores[28] were also assessed. Patient-reported outcomes included change on the Caregiver Strain Questionnaire.[29] Efficacy assessments were conducted at baseline (day 1) and days 4, 7, 14, and 21, with the exception of CGAS, which was performed at days 1 and 21.

Safety and Tolerability Evaluations

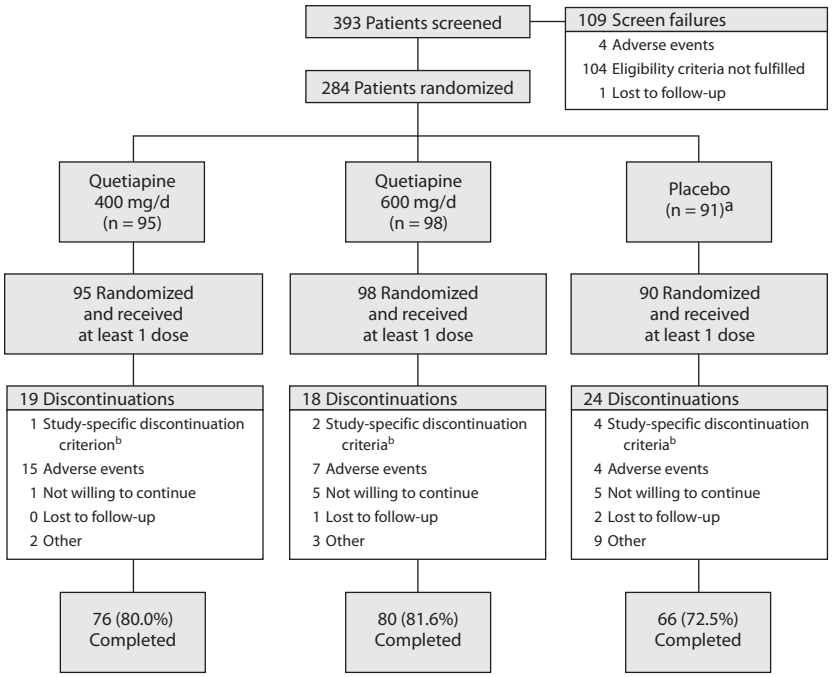
Safety and tolerability evaluations included incidence of adverse events and event-related withdrawals. Spontaneously reported adverse events were classified by the Medical Dictionary for Regulatory Activities (MedDRA) and rated as medication related by investigators' judgment.

Incidents of treatment-emergent depression (CDRS-R total score ≥ 40) were evaluated at end point in patients with baseline scores < 40. Clinical and laboratory safety parameters were determined at a central laboratory. Extrapyramidal symptoms were assessed by adverse event rates, Simpson-Angus Scale,[30] Barnes Akathisia Rating Scale,[31] and Abnormal Involuntary Movement Scale,[32] and benztropine use to treat extrapyramidal symptoms. Adverse events, weight, vital signs, and extrapyramidal symptoms scores were assessed at baseline and days 4, 7, 14, and 21. Chemistry and hematology parameters were assessed at screening and day 21 or final visit.

Statistical Analyses

Efficacy analyses were performed on the modified intent-to-treat (ITT) population, including patients with baseline and at least 1 postbaseline assessment. Mean changes in YMRS total score from baseline to day 21 were analyzed by using mixed-model, repeated-measures (MMRM) analysis, with baseline score as covariate and age stratum, treatment, visit, and visit-by-treatment interaction as fixed effects. An analysis of covariance (ANCOVA) with last-observation-carried-forward (LOCF) imputation was conducted to support MMRM analyses. The Simes-Hommel step-up procedure controlled for multiplicity of 2 comparisons (quetiapine 400 mg/d and 600 mg/d) with placebo. Change in CGI-BP-Severity of Illness score was also assessed by MMRM. Changes in CDRS-R and Overt Aggression Scale-Modified scores were assessed by ordinal logistic regression model, with age stratum, treatment, and baseline measure as variables. The CGI-BP-Global Improvement was assessed by generalized estimating equation analysis, with CGI-BP-Severity of Illness score as a covariate and factors for treatment, visit, visit-by-treatment interaction. Change in CGAS score was assessed by ANCOVA.

Figure 1. Disposition of Children and Adolescents With Bipolar I Disorder in the Screening and Randomized Treatment Phases for the Quetiapine 400 mg/d, Quetiapine 600 mg/d, and Placebo Groups



[a]Includes 1 patient who was unable to attend visits and discontinued the study before receiving study medication.
[b]Study-specific discontinuation criteria include withdrawal of informed consent, severe noncompliance (as judged by investigators), symptom deterioration, or inability to tolerate the assigned dose.

All statistical comparisons used 2-sided tests (significance level, $P < .05$).

Safety and tolerability analyses were conducted on the safety population, including all patients receiving at least 1 dose of study medication.[33] Details of safety analyses are reported in Supplementary eAppendix 2.

Sample sizes were calculated to provide at least 85% power to detect a difference of 6 points between the quetiapine 400 mg/d or 600 mg/d group and placebo for the primary efficacy analysis.

RESULTS

Patients and Disposition

Of 393 patients screened, 284 were randomly assigned to treatment (Figure 1). Most screen failures were due to failure to fulfill eligibility criteria. Of 284 randomized patients, 283 were included in the safety population and 277 in the ITT population (n = 93, quetiapine 400 mg/d; n = 95, quetiapine 600 mg/d; n = 89, placebo).

Treatment groups were well balanced for baseline clinical and demographic characteristics, although Overt Aggression Scale-Modified total scores were higher in the quetiapine groups (Table 1).

Study completion rates were 80.0%, 81.6%, and 72.5% in the quetiapine 400 mg/d, quetiapine 600 mg/d, and placebo groups, respectively. The most common reasons for study withdrawal were adverse events in both quetiapine groups (15.8%, quetiapine 400 mg/d; 7.1%, quetiapine 600 mg/d) and "other" (primarily, lack of efficacy) in the placebo group (10.0%).

Rates of treatment compliance assessed by returned-tablet count were high (92.7%, quetiapine 400 mg/d; 92.9%, quetiapine 600 mg/d; 92.3%, placebo). Proportions of patients using psychostimulants for comorbid ADHD symptoms were comparable between the quetiapine 600 mg/d (13.3%) and placebo (12.2%) groups and nonsignificantly higher in the quetiapine 400 mg/d group (20.0%).

Efficacy

Quetiapine at both 400 mg/d and 600 mg/d was associated with significantly greater improvements than placebo in YMRS total score. Least squares mean change in YMRS score from baseline to day 21 by MMRM analysis was –14.25 (standard error [SE] = 0.96; 95% CI, –16.15 to –12.35) with quetiapine 400 mg/d, –15.60 (SE = 0.97; 95% CI, –17.51 to –13.70) with quetiapine 600 mg/d, and –9.04 (SE = 1.12; 95% CI, –11.24 to –6.84) with placebo ($P < .001$, each quetiapine dose vs placebo; observed cases). Significantly greater improvements in YMRS score change versus placebo were first observed at day 4 with quetiapine 400 mg/d ($P = .015$) and day 7 with quetiapine 600 mg/d ($P < .001$).

Analyses of covariance utilizing LOCF imputation supported MMRM analyses. Least squares mean change in YMRS total score at day 21 using LOCF analysis was –13.42 (SE = 0.99;

Table 1. Demographic and Disease Characteristics at Baseline in Children and Adolescents Treated With Quetiapine 400 mg/d, Quetiapine 600 mg/d, or Placebo (ITT population)

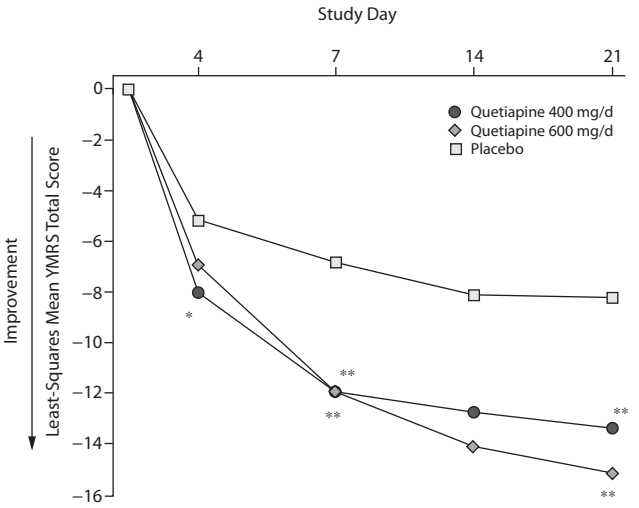
	Quetiapine 400 mg/d (n = 93)[a]		Quetiapine 600 mg/d (n = 95)[b]		Placebo (n = 89)	
Characteristic	n	%	n	%	n	%
Age, y						
10–12	43	46.2	42	44.2	36	40.4
13–17	50	53.8	53	55.8	53	59.6
Sex, female	46	49.5	40	42.1	35	39.3
Race						
Black	12	12.9	14	14.7	12	13.5
White	73	78.5	73	76.8	66	74.2
Asian	0	0	0	0	1	1.1
Other	8	8.6	8	8.4	10	11.2
Current or past history of co-occurring ADHD	49	52.7	40	42.1	35	39.3
Most recent episode severe, with psychotic features	6	6.5	6	6.3	7	7.9
Most recent episode severe, without psychotic features	14	15.1	16	16.8	14	15.7
Subject hospitalized previously for suicide attempt	5	5.4	4	4.2	1	1.1
Family members with known diagnosis of bipolar disorder						
Yes	49	52.7	64	67.4	60	67.4
No	41	44.1	31	32.6	29	32.6
Missing	3	3.2	0	0	0	0
Previous exposure to quetiapine						
Yes	25	26.9	16	16.8	15	16.9
No	68	73.1	79	83.2	74	83.1
	Mean	SD	Mean	SD	Mean	SD
Age, y	13.11	2.16	13.15	2.18	13.31	2.14
Weight, kg	59.71	18.08	60.08	17.83	62.48	19.42
BMI (kg/m^2)	23.50	5.31	23.38	4.77	24.14	5.67
YMRS score	29.4	5.8	29.6	6.4	30.7	5.9
CDRS-R score	30.5	10.2	30.4	9.6	30.2	9.9
CGI-BP Severity of Illness score	4.7	0.8	4.6	0.7	4.6	0.6
CGAS score	45.5	9.8	45.4	10.0	45.5	9.3
OAS-M score	80.7	105.2	96.7	121.4	71.0	69.4
CGSQ score	2.4	0.9	2.4	0.8	2.5	0.6

[a]Includes 1 patient (1.1%) with mixed episode. [b]Includes 4 patients (4.2%) with mixed episodes. Only patients with mania were intended to be enrolled in the study.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BMI = body mass index, CDRS-R = Children's Depression Rating Scale-Revised, CGAS = Children's Global Assessment Scale, CGI-BP = Clinical Global Impressions-Bipolar Version, CGSQ = Caregiver Strain Questionnaire, ITT = intent to treat, OAS-M = Overt Aggression Scale-Modified, YMRS = Young Mania Rating Scale.

95% CI, –15.37 to –11.48; $P < .001$ vs placebo) with quetiapine 400 mg/d, –15.18 (SE = 0.99; 95% CI, –17.10 to –13.25; $P < .001$ vs placebo) with quetiapine 600 mg/d, and –8.28 (SE = 1.02; 95% CI, –10.28 to –6.28) with placebo (Figure 2). Last-observation-carried-forward analyses demonstrated significant improvements in YMRS total score versus placebo at day 4 with quetiapine 400 mg/d ($P = .035$) and at day 7 with quetiapine 600 mg/d ($P < .001$) (Figure 2). Effect sizes (ie, improvement with quetiapine vs placebo divided by pooled standard deviation) based on LOCF analyses were 0.539 for quetiapine 400 mg/d and 0.867 for quetiapine 600 mg/d.

Figure 2. Least Squares Mean Change in YMRS Total Score From Baseline to Day 21 in Children and Adolescents Treated With Quetiapine 400 mg/d, Quetiapine 600 mg/d, or Placebo (LOCF, ITT population)



*$P < .05$ versus placebo, **$P < .001$ versus placebo.

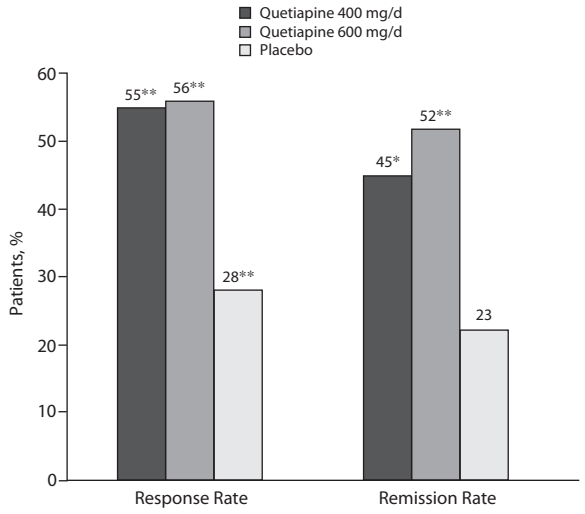
Abbreviations: ITT = intent to treat, LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

Comparisons of YMRS total score change indicated that quetiapine was equally efficacious in patients subcategorized by age (10–12 vs 13–17 years), gender, ADHD status, or psychostimulant use. Least squares mean changes in YMRS total score from baseline to day 21 by MMRM analysis in children and adolescents, respectively, were –13.5 and –14.9 with quetiapine 400 mg/d, –17.1 and –14.4 with quetiapine 600 mg/d, and –8.7 and –9.4 with placebo. There was a significant difference ($P < .05$) between both doses of quetiapine and placebo in the 13- to 17-year age group and between quetiapine 600 mg/d and placebo in the 10- to 12-year age group. Mean changes in YMRS total score using LOCF analyses were similar to changes analyzed by MMRM: –12.2 and –14.1, respectively, in children and adolescents treated with quetiapine 400 mg/d, –16.2 and –14.2 with quetiapine 600 mg/d, and –7.7 and –10.1 with placebo.

Mean changes in YMRS total score from baseline to day 21 using MMRM in boys and girls, respectively, were –14.3 and –16.4 with quetiapine 400 mg/d, –16.2 and –15.1 with quetiapine 600 mg/d, and –10.3 and –9.8 with placebo. Mean changes in YMRS total score in boys and girls, respectively, using LOCF analyses were –12.5 and –13.9 with quetiapine 400 mg/d, –15.6 and –14.4 with quetiapine 600 mg/d, and –8.3 and –9.0 with placebo.

Mean changes in YMRS total score from baseline to day 21 using MMRM in patients with comorbid ADHD were significantly greater with quetiapine than with placebo: –14.3, –16.6, and –9.3 for quetiapine 400 mg/d ($P < .05$ vs placebo), quetiapine 600 mg/d ($P < .001$ vs placebo), and placebo, respectively. Similar results were noted in patients without ADHD: mean changes in YMRS total score were –14.3, –14.9, and –8.8 for quetiapine 400 mg/d ($P < .05$ vs

Figure 3. Response and Remission Rates at Day 21 in Children and Adolescents Treated With Quetiapine 400 mg/d, Quetiapine 600 mg/d, or Placebo (LOCF, ITT population)[a]



[a]Response equals ≥ 50% reduction in Young Mania Rating Scale (YMRS) total score from baseline to day 21; remission equals YMRS total score ≤ 12 at day 21.
*$P < .01$ versus placebo, **$P < .001$ versus placebo.
Abbreviations: ITT = intent-to-treat, LOCF = last observation carried forward.

placebo), quetiapine 600 mg/d ($P < .01$ vs placebo), and placebo, respectively. Last-observation-carried-forward analyses confirmed assessments by MMRM in these subgroups. Mean changes in YMRS total score by LOCF were significantly greater with quetiapine than placebo, both in patients with comorbid ADHD (–13.7, –15.9, and –8.3 for quetiapine 400 mg/d, quetiapine 600 mg/d, and placebo, respectively; $P = .007$ and $< .001$ for quetiapine 400 and 600 mg/d, respectively, vs placebo) and in patients without comorbid ADHD (–13.3, –14.7, and –8.2 for quetiapine 400 mg/d, quetiapine 600 mg/d, and placebo, respectively; $P = .007$ and $< .001$, respectively, vs placebo). Mean changes in YMRS total score from baseline to day 21 (LOCF, ITT) in psychostimulant users and nonusers, respectively, were –12.9 and –13.3 with quetiapine 400 mg/d, –13.2 and –15.5 with quetiapine 600 mg/d, and –9.5 and –8.4 with placebo. Differences between the quetiapine and the placebo groups were not significant in the psychostimulant user group but were significant in the nonuser group ($P < .01$ for both doses).

Both quetiapine doses were associated with significantly greater response and remission rates than placebo at day 21 (Figure 3).

Raw mean (SD) changes in CDRS-R total score from baseline to day 21 were –5.2 (8.47) with quetiapine 400 mg/d, –6.2 (7.56) with quetiapine 600 mg/d, and –3.8 (8.02) with placebo (ordinal logistic regression; observed cases). Changes in CDRS-R total score differed significantly between quetiapine 600 mg/d and placebo groups ($P < .05$).

Least squares mean changes in CGI-BP-Severity of Illness score at day 21 were –1.55 (SE = 0.14; 95% CI, –1.83 to –1.27), –1.62 (SE = 0.13; 95% CI, –1.88 to –1.37), and –0.98 (SE = 0.14; 95% CI, –1.26 to –0.71) with quetiapine 400 mg/d, 600 mg/d, and placebo, respectively ($P = .005$, quetiapine 400 mg/d; $P < .001$, quetiapine 600 mg/d vs placebo; MMRM, observed cases). Significant improvements in CGI-BP-Severity of Illness score versus placebo were first observed at day 7 with both quetiapine 400 mg/d ($P = .009$) and quetiapine 600 mg/d ($P = .003$).

The CGI-BP-Global Improvement scores indicated that 23.7% and 19.8% of patients in the quetiapine 400 mg/d and 600 mg/d group, respectively, were "very much improved" at day 21 compared with 13.2% with placebo; another 32.9%, 45.7%, and 20.6%, respectively, were "much improved" (observed cases, nonmissing values). Last-observation-carried-forward analyses of CGI-BP-Global Improvement scores indicated similar improvements to the observed case analyses, with 19.4% and 20.0% of patients in the quetiapine 400 mg/d and 600 mg/d group, respectively, "very much improved" at day 21, compared with 11.2% with placebo. The odds of achieving improvement at day 21 (CGI-BP-Global Improvement scores "very much improved" or "much improved") were significantly higher with quetiapine 400 mg/d (odds ratio [OR] = 2.43; 95% CI, 1.24 to 4.76; $P = .010$) and quetiapine 600 mg/d (OR = 3.86; 95% CI, 1.97 to 7.56; $P < .001$) versus placebo.

Mean changes in CGAS total score from baseline to day 21 were 12.19 (SE = 1.30; 95% CI, 9.64 to 14.75) with quetiapine 400 mg/d, 14.61 (SE = 1.32; 95% CI, 12.00 to 7.211) with quetiapine 600 mg/d, and 7.62 (SE = 1.36; 95% CI, 4.95 to 10.29) with placebo (LOCF, observed cases). Changes in CGAS total score in the quetiapine 400 mg/d and 600 mg/d groups were significantly different from placebo ($P < .05$ and $P < .001$, respectively).

Because the assumption of normality did not hold true for changes from baseline, ordinal logistic regression analyses were used to compare frequencies of patients in predefined Overt Aggression Scale-Modified score categories for each treatment group. On the basis of these analyses, no significant difference was observed in the quetiapine 400 mg/d (OR = 0.60; 95% CI, 0.31 to 1.16; $P = .127$) or quetiapine 600 mg/d groups (OR = 0.53; 95% CI, 0.27 to 1.04; $P = .065$) compared with placebo for lessening agitation and aggression.

Least squares mean changes in the Caregiver Strain Questionnaire total score from baseline to day 21 were –0.63 (SE = 0.08; 95% CI, –0.79 to –0.47) with quetiapine 400 mg/d, –0.65 (SE = 0.08; 95% CI, –0.81 to –0.49) with quetiapine 600 mg/d, and –0.47 (SE = 0.08; 95% CI, –0.64 to –0.31) with placebo (LOCF, observed cases). No significant differences versus placebo were observed with quetiapine 400 mg/d ($P = .177$) or quetiapine 600 mg/d ($P = .133$) for relieving overall caregiver burden.

Safety and Tolerability

The most common adverse events in quetiapine-treated patients were somnolence, sedation, dizziness, and headache (Table 2). Most events were mild to moderate in intensity. Treatment discontinuations due to adverse events occurred

Table 2. Incidence of Common Adverse Events (frequency ≥ 5% in any quetiapine group) in Children and Adolescents Treated With Quetiapine 400 mg/d, Quetiapine 600 mg/d, or Placebo (safety population)

	Quetiapine 400 mg/d (n = 95)		Quetiapine 600 mg/d (n = 98)		Placebo (n = 90)	
Adverse Event	n	%	n	%	n	%
Somnolence	27	28.4	31	31.6	9	10.0
Sedation	22	23.2	25	25.5	4	4.4
Dizziness	18	18.9	17	17.3	2	2.2
Headache	15	15.8	13	13.3	14	15.6
Nausea	6	6.3	10	10.2	4	4.4
Fatigue	13	13.7	9	9.2	4	4.4
Increased appetite	9	9.5	9	9.2	1	1.1
Tachycardia	5	5.3	8	8.2	0	0
Dry mouth	7	7.4	7	7.1	0	0
Vomiting	8	8.4	7	7.1	3	3.3
Nasal congestion	3	3.2	6	6.1	2	2.2
Weight increase	6	6.3	6	6.1	0	0
Irritability	3	3.2	5	5.1	1	1.1

Table 3. Incidence of Serious Adverse Events in Children and Adolescents Treated With Quetiapine 400 mg/d, Quetiapine 600 mg/d, or Placebo (safety population)[a]

	Quetiapine 400 mg/d (n = 95)		Quetiapine 600 mg/d (n = 98)		Placebo (n = 90)	
Serious Adverse Event	n	%	n	%	n	%
Bipolar disorder exacerbation	3	3.2	1	1.0	3	3.3
Suicidal ideation	1	1.1	0	0	0	0
Mania	1	1.1	0	0	0	0
Aggression	1	1.1	1	1.0	0	0
Syncope	1	1.1	0	0	0	0
Staphylococcal infection	0	0	1	1.0	0	0
Drug rash	0	0	1	1.0	0	0

[a]In total, 12 patients reported 14 serious adverse events.

in 15.8%, 7.1%, and 4.4% of patients receiving quetiapine 400 mg/d, quetiapine 600 mg/d, and placebo, respectively. Events most commonly associated with discontinuation were sedation (5.3%), somnolence (3.2%), syncope (2.1%), fatigue (2.1%), irritability (2.1%), and exacerbation of bipolar disorder (2.1%) in the quetiapine 400 mg/d group; fatigue (2.0%) in the quetiapine 600 mg/d group; and exacerbation of bipolar disorder (2.2%) in the placebo group.

Serious adverse events were reported in 5.3% (n = 5) of the quetiapine 400 mg/d, 4.1% (n = 4) of the quetiapine 600 mg/d, and 3.3% (n = 3) of the placebo group. Most serious adverse events were related to underlying psychiatric disorders (Table 3). The incidence of treatment-emergent depression (CDRS-R score ≥ 40) was 2.1%, 1.0%, and 3.3% in the respective groups.

Mean (SD) change in body weight was 1.7 (1.98) kg, 1.7 (2.34) kg, and 0.4 (1.72) kg in the quetiapine 400 mg/d, quetiapine 600 mg/d, and placebo groups, respectively (observed cases). A weight increase ≥ 7% between baseline and day 21 was reported in 14.5%, 9.9%, and 0% of the respective groups.

Mean changes from baseline to final visit in aspartate aminotransferase, alanine aminotransferase, fasting glucose, insulin, total cholesterol, low-density lipoprotein cholesterol, triglycerides, thyroid-stimulating hormone, and prolactin levels were greater in the quetiapine groups than the placebo group (Table 4). Potentially clinically significant shifts in total cholesterol, low-density lipoprotein cholesterol, and triglyceride concentrations were more frequent in the quetiapine groups (Table 5).

One patient in each quetiapine dose group experienced a potentially clinically significant elevation of glucose at final visit (126 mg/dL and 131 mg/dL), although neither patient was confirmed as fasting at the time of glucose elevation. Four patients in the quetiapine groups experienced adverse events potentially related to diabetes, including thirst (2 patients, quetiapine 400 mg/d group), increase of blood insulin (2 patients, quetiapine 400 mg/d and 600 mg/d groups), and increase of glycosylated hemoglobin (1 patient, quetiapine 600 mg/d group). None of these elevations resulted in study discontinuation.

Changes in free or total thyroxine concentrations to potentially clinically significant low values occurred more frequently in the quetiapine groups versus placebo; these changes were not associated with changes in thyroid stimulating hormone concentrations. Changes in prolactin from normal to high concentrations were observed more frequently in the quetiapine groups than placebo group (Table 5). No adverse events appeared in relation to hyperprolactinemia.

Hematology values and adverse event reports indicated no clinically significant differences between treatment groups. Incidences of potentially clinically significant shifts in hematology values are in Table 6.

Mean changes in blood pressure (systolic and diastolic, supine and standing) were similar across treatment groups. Mean changes in pulse rate were greater in quetiapine groups, eg, mean (SD) changes in standing pulse rate were 9.6 (15.24), 11.3 (18.88), and 0.1 (12.66) beats per minute in the quetiapine 400 mg/d, quetiapine 600 mg/d, and placebo groups, respectively. Potentially clinically significant shifts in blood pressure, pulse rate, and electrocardiogram parameters are in Table 7.

Tachycardia was reported as an adverse event in 5.3%, 8.2%, and 0% of patients in the quetiapine 400 mg/d, quetiapine 600 mg/d, and placebo groups, respectively. Four patients (2 patients in each quetiapine group) experienced an adverse event of syncope within the first 8 days. This event led to discontinuation by both patients in the quetiapine 400 mg/d group; syncope resolved on the same day in both patients treated with quetiapine 600 mg/d and did not lead to discontinuation. Of these 4 patients, 1 took concomitant psychostimulants.

Adverse events potentially associated with extrapyramidal symptoms, including akathisia, restlessness, and tremor, occurred in 4.2%, 3.1%, and 1.1% of patients in the quetiapine 400 mg/d, quetiapine 600 mg/d, and placebo groups, respectively. All events were judged mild to moderate in intensity. Rates of anticholinergic medication use were 5.3%, 6.1%, and 11.1%, respectively. Changes in Simpson-Angus

Table 4. Changes From Baseline to Final Visit in Selected Chemistry Parameters in Children and Adolescents Treated With Quetiapine 400 mg/d, Quetiapine 600 mg/d, or Placebo (safety population)

	Quetiapine 400 mg/d (n = 95)			Quetiapine 600 mg/d (n = 98)			Placebo (n = 90)		
Parameter	n	Mean	SD	n	Mean	SD	n	Mean	SD
Aspartate transaminase, IU/L	90	1.81	7.95	87	2.60	11.66	79	1.15	5.55
Alanine aminotransferase, IU/L	90	3.04	11.67	87	6.63	21.31	79	0.41	9.78
Creatinine, mg/dL	90	0.01	0.09	87	0.02	0.15	79	0.01	0.10
Blood urea nitrogen, mg/dL	90	−0.21	3.35	87	−0.87	3.05	79	0.72	3.39
Glucose, fasting, mg/dL	87	3.48	11.50	83	3.76	13.10	81	−1.17	11.03
Insulin, μIU/L	76	6.75	46.00	83	10.51	26.58	76	−1.38	23.90
Total cholesterol, mg/dL	90	7.81	23.84	87	7.61	22.61	79	−3.33	23.89
Low-density lipoprotein cholesterol, mg/dL	90	5.64	21.29	87	2.89	19.02	79	−0.48	18.52
High-density lipoprotein cholesterol, mg/dL	90	−0.06	7.73	87	−1.43	7.57	79	−1.04	7.96
Triglycerides, mg/dL	90	11.17	58.54	87	30.57	64.59	79	−8.73	60.11
Thyroid stimulating hormone, μIU/mL	81	−0.11	1.19	85	0.20	1.12	80	−0.11	1.11
Free thyroxine, μg/dL	82	−0.16	0.15	86	−0.17	0.17	82	−0.00	0.15
Total thyroxine, μg/dL	82	−1.43	1.32	86	−1.77	1.57	82	0.02	1.21
Prolactin, ng/mL	82	2.84	13.28	86	1.86	11.26	82	−1.15	9.17

Table 5. Incidence of Potentially Clinically Significant Shifts in Chemistry Values From Normal at Baseline in Children and Adolescents Treated With Quetiapine 400 mg/d, Quetiapine 600 mg/d, or Placebo (safety population)

		Shifts					
		Quetiapine 400 mg/d (n = 95)		Quetiapine 600 mg/d (n = 98)		Placebo (n = 90)	
Parameter	Potentially Significant Values	n (%)	n[a]	n (%)	n[a]	n (%)	n[a]
Aspartate transaminase	≥ 3 × ULN	0 (0)	90	0 (0)	87	0 (0)	79
Alanine aminotransferase	≥ 3 × ULN	0 (0)	90	0 (0)	87	0 (0)	79
Creatinine	≥ 1.357 mg/dL	0 (0)	90	1 (1.2)	85	0 (0)	79
Blood urea nitrogen	≥ 21 mg/dL	0 (0)	95	0 (0)	98	2 (2.6)	90
Glucose, fasting	Fasting ≤ 45 mg/dL; ≥ 126 mg/dL	1 (1.1)	86	1 (1.2)	81	0 (0)	81
Total cholesterol	≥ 170 mg/dL	15 (27.3)	55	15 (27.8)	54	2 (4.6)	44
Low-density lipoprotein cholesterol	≥ 160 mg/dL	0 (0)	90	1 (1.2)	85	0 (0)	79
High-density lipoprotein cholesterol	≤ 40 mg/dL	2 (2.6)	77	13 (16.9)	77	4 (6.6)	61
Triglycerides	≥ 150 mg/dL	14 (18.4)	76	15 (20.6)	73	8 (13.3)	60
Thyroid stimulating hormone	> 5 μIU/mL	2 (2.6)	77	2 (2.4)	83	1 (1.3)	78
Free thyroxine	< 0.8 × LLN; > 1.2 × ULN	1 (1.2)	82	0 (0)	85	0 (0)	82
Total thyroxine	< 0.8 × LLN; > 1.2 × ULN	0 (0)	82	3 (3.5)	85	0 (0)	82
Prolactin	> 26 ng/mL females; > 20 ng/mL males	12 (15.8)	76	10 (12.3)	81	2 (2.6)	78

[a]Total number of patients with values within the normal range at baseline and at least 1 postbaseline value. The study protocol specified fasting blood draws (fasting was defined as ≥ 8 hours between time of last meal and time of blood draw). Not all patients in this study were confirmed fasting.
Abbreviations: LLN = lower limit of normal, ULN = upper limit of normal.

Scale, Barnes Akathisia Rating Scale, and Abnormal Involuntary Movement Scale scores from baseline to day 21 were small and similar across groups.

Approximately 15% of patients received a concomitant psychostimulant (19 patients [20.0%], quetiapine 400 mg/d group; 13 patients [13.3%], quetiapine 600 mg/d group; 11 patients [12.2%], placebo group). Among patients who experienced potentially clinically significant shifts in vital signs, psychostimulant use was more common in both quetiapine groups (18.2% with 400 mg/d and 13.8% with 600 mg/d) compared with placebo (8.3%). Common adverse events in the quetiapine 600 mg/d group (including nausea, dizziness, sedation, and increased appetite) were more frequent in patients taking psychostimulants versus those not taking psychostimulants. No such differences in adverse event rate were noted in the quetiapine 400 mg/d or placebo groups.

In post hoc analysis using the Columbia-Suicide Severity Rating Scale,[33] 2 patients in the quetiapine 400-mg/d group demonstrated suicidal behavior and 2 others were classified with possible suicidal events. In the quetiapine 600-mg/d group, 2 patients had possible suicidal events and another experienced suicidal ideation.

Higher incidences of increased appetite (14.0% vs 5.8%), increased pulse rate (9.4% vs 4.8%), suicidal behavior/ideation (5.9% vs 1.9%), and syncope (3.5% vs 0.9%) were observed in younger (aged 10–12 years) compared with older patients (aged 13–17 years) in quetiapine dose groups combined. Age-related differences in tolerability were not observed in the placebo group.

DISCUSSION

This is the first large, randomized, placebo-controlled study to evaluate quetiapine in the acute treatment of youth

Table 6. Incidence of Potentially Clinically Significant Shifts in Hematology Values From Normal at Baseline in Children and Adolescents Treated With Quetiapine 400 mg/d, Quetiapine 600 mg/d, or Placebo (safety population)

		Shift to Low Value						Shift to High Value					
		Quetiapine 400 mg/d (n = 95)		Quetiapine 600 mg/d (n = 98)		Placebo (n = 90)		Quetiapine 400 mg/d (n = 95)		Quetiapine 600 mg/d (n = 98)		Placebo (n = 90)	
Parameter	Potentially Significant Values	n	%	n	%	n	%	n	%	n	%	n	%
Hematocrit	≤ 0.35; ≥ 0.50 vol fraction	0	0	7	8.9	1	1.4	1	1.2	0	0	2	2.8
Hemoglobin	≤ 115 g/L; ≥ 172 g/L	2	2.3	2	2.4	0	0	0	0	0	0	0	0
Total red blood cell count	$\leq 3 \times 10^{12}$ cells/L; $\geq 6 \times 10^{12}$ cells/L	0	0	0	0	0	0	0	0	0	0	1	1.2
Platelet count	$\leq 100 \times 10^{9}$ cells/L; $\geq 600 \times 10^{9}$ cells/L	0	0	0	0	0	0	0	0	0	0	0	0
Total white blood cell count	$\leq 3 \times 10^{9}$ cells/L; $\geq 16 \times 10^{9}$ cells/L	0	0	0	0	1	1.3	0	0	0	0	0	0
Neutrophils	≤ 15%	3	3.6	4	4.9	2	2.5	…	…	…	…	…	…
Eosinophils	≥ 10%	…	…	…	…	…	…	2	2.3	0	0	0	0
Basophils	$\geq 0.5 \times 10^{9}$ cells/L	…	…	…	…	…	…	0	0	0	0	0	0
Lymphocytes	$\leq 0.5 \times 10^{9}$ cells/L; $\geq 6 \times 10^{9}$ cells/L	0	0	0	0	0	0	0	0	0	0	0	0
Monocytes	$\geq 1.4 \times 10^{9}$ cells/L	…	…	…	…	…	…	0	0	0	0	0	0

Table 7. Incidence of Potentially Clinically Significant Shifts in Vital Signs and Electrocardiogram (ECG) Parameters From Normal at Baseline in Children and Adolescents Treated With Quetiapine 400 mg/d, Quetiapine 600 mg/d, or Placebo (safety population)[a]

		Shift to Low Value						Shift to High Value					
		Quetiapine 400 mg/d (n = 95)		Quetiapine 600 mg/d (n = 98)		Placebo (n = 90)		Quetiapine 400 mg/d (n = 95)		Quetiapine 600 mg/d (n = 98)		Placebo (n = 90)	
Variable	Potentially Significant Values	n	%	n	%	n	%	n	%	n	%	n	%
Vital signs													
Supine systolic blood pressure	Increase and decrease ≥ 20 mm Hg	2	2.4	2	2.3	0	0	6	7.1	4	4.5	1	1.3
Supine diastolic blood pressure	Increase ≥ 30 mm Hg; decrease ≥ 20 mm Hg	0	0	0	0	2	2.7	1	1.2	4	5.1	3	4.1
Supine pulse	Increase and decrease ≥ 15 mm Hg	0	0	0	0	0	0	1	1.1	2	2.2	0	0
Standing systolic blood pressure	Increase and decrease ≥ 20 mm Hg	3	3.6	6	6.7	2	2.4	9	10.7	2	2.2	4	4.8
Standing diastolic blood pressure	Increase ≥ 30 mm Hg; decrease ≥ 20 mm Hg	2	2.6	0	0	2	2.7	9	11.5	10	12.0	14	18.7
Standing pulse	Increase and decrease ≥ 15 bpm	0	0	0	0	0	0	13	14.3	10	11.1	1	1.2
ECG parameters													
Heart rate	Increase and decrease ≥ 15 bpm	0	0	1	1.2	0	0	1	1.1	2	2.4	0	0
PR interval	≥ 200 msec	…	…	…	…	…	…	0	0	0	0	1	1.2
QRS interval	Increase ≥ 100 msec; decrease ≤ 50 msec	0	0	0	0	0	0	0	0	0	0	0	0
QT interval	Increase ≥ 60 msec	…	…	…	…	…	…	0	0	0	0	0	0
QTc interval (Fridericia)	Increase ≥ 15% of baseline	…	…	…	…	…	…	0	0	0	0	0	0

[a]Percentages are based on all patients with values at baseline and day 21.
Abbreviation: bpm = beats per minute.

with bipolar I disorder with manic episodes. Quetiapine at both doses (400 mg/d and 600 mg/d) was significantly more effective than placebo in treating manic symptoms, based on the primary efficacy measure of change in YMRS total score over 3 weeks.

Quetiapine offered rapid onset of effect, with superiority over placebo by day 4 in the 400 mg/d group and day 7 in the 600 mg/d group. Improvements in YMRS score with quetiapine were broadly equivalent between children (aged 10–12 years) and adolescents (aged 13–17 years), boys and girls, patients with or without co-occurring ADHD, and patients with or without current psychostimulant exposure.

This placebo-controlled study supports and extends findings from previous studies of quetiapine in adolescents with manic or mixed episodes of bipolar disorder, including a randomized, double-blind, placebo-controlled trial of quetiapine combined with divalproex and a randomized pilot study of quetiapine versus divalproex monotherapy.[16,17] Similar efficacy outcomes versus placebo are reported in 3- to 4-week studies of olanzapine (2.5–20 mg/d), risperidone (0.5–2.5 mg/d or 3–6 mg/d), and aripiprazole (10 or 30 mg/d) in adolescents with bipolar mania.[11,14,15]

The safety profile of quetiapine in this trial is consistent with the profile reported in adolescents and adults with acute manic symptoms of bipolar disorder.[17,34] Adverse events most commonly associated with quetiapine included somnolence, sedation, dizziness, and headache, and these were, in most cases, mild to moderate in intensity.

Mean weight change at day 21 was greater in the quetiapine groups than placebo group, consistent with adult studies of acute bipolar mania.[34] Changes in laboratory values in the quetiapine group included total cholesterol, fasting glucose, insulin, prolactin, and measures of liver and thyroid function. Incidences of potentially clinically significant shifts in laboratory, hematologic, and vital sign measures were low. Although no significant differences in these parameters

were noted between groups in this study, current recommendations are to measure lipid levels and blood pressure in children and adolescents at the beginning and periodically during treatment.[35]

One of the strengths of this study is that 45% of patients had a comorbid diagnosis of ADHD at baseline and approximately 15% took concomitant psychostimulants. Incidences of adverse events in the quetiapine groups were similar in patients with or without psychostimulant use, suggesting that psychostimulants may pose no additional health risk in this population, although the sizes of patient subgroups were small.

Post hoc analysis using the Columbia-Suicide Severity Rating Scale identified 4 patients in the quetiapine 400-mg/d group and 3 patients in the 600-mg/d group with events possibly related to suicidality. Although no firm relationship between treatment and suicidal behavior/ideation was established, it should be noted that the FDA has issued a boxed warning[35] for increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (including quetiapine) for major depressive disorder and other psychiatric disorders.

The safety profile of quetiapine in children was broadly similar to that in adolescents. However, potentially elevated incidences of increased appetite, increased pulse heart rate, suicidal behavior/ideation, and syncope in the younger age group may indicate increased vulnerability to adverse events. An open-label investigation of the long-term safety of quetiapine that includes patients enrolled in the current study is the topic of a subsequent manuscript (ClinicalTrials.gov identifier: D1441C00150).

Limitations that may be considered when interpreting the outcomes of this study include the short study duration, the predominantly white population, the exclusion of patients with a current comorbidity other than ADHD, and the rapid titration to fixed quetiapine doses, which differs from the flexible dosing commonly utilized in clinical practice. The potential tolerability differences between children and adolescents, discussed above, may be influenced by the use of a flexibly dosed protocol. The study was not designed to include patients with mixed episodes, which limits the generalizability of the findings.

Two additional factors influence interpretation of the efficacy results: the effect of residual symptomatology on YMRS scores at study completion, and the meaningful symptom changes in the placebo group, which impacted the degree of symptom amelioration attributable to active medication. Despite these limitations, the large population size and the broad range of efficacy and safety measures investigated support a role for this study in guiding clinical practice.

In conclusion, quetiapine at 400 mg/d and 600 mg/d was significantly more effective than placebo for treating acute manic symptoms in youth with bipolar I disorder. Quetiapine at these doses was generally well tolerated and adverse events were consistent with the profile of quetiapine in adults with bipolar disorder.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), divalproex (Depakote and others), hydroxyzine (Vistaril and others), lithium (Lithobid and others), lorazepam (Ativan and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others).

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Study participants: The Trial 149 Study Investigators are listed in Supplementary eAppendix 1.

Potential conflicts of interest: **Drs Pathak** and **Acevedo** are employees of AstraZeneca. **Dr Findling** receives or has received research support, acted as a consultant, and/or served on a speaker's bureau for Abbott, Addrenex, Alexza, AstraZeneca, Biovail, Bristol-Myers Squibb, Dainippon Sumitomo, Forest, GlaxoSmithKline, Johnson & Johnson, KemPharm Lilly, Lundbeck, Merck, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Rhodes Pharmaceuticals, Sanofi-Aventis, Schering-Plough, Seaside Therapeutics, Sepracor, Shire, Solvay, Sunovion, Supernus, Transcept, Validus, and Wyeth. **Dr Earley** and **Ms Stankowski** are former employees of AstraZeneca. **Dr DelBello** receives or has received research support from AstraZeneca, Eli Lilly, Johnson & Johnson, Shire, Janssen, Pfizer, Bristol-Myers Squibb, Repligen, Martek, Somerset, NIDA, National Institute of Mental Health, NIAAA, NARSAD, Thrasher Foundation, GlaxoSmithKline, and Sumitomo; has served on lecture bureau of Bristol-Myers Squibb and Merck; and has been a consultant to, has served on advisory boards of, or has received honoraria from GlaxoSmithKline, Eli Lilly, Schering-Plough, and Merck.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

THE JOURNAL OF CLINICAL PSYCHIATRY

Supplementary Material

Article Title: Efficacy and Safety of Quetiapine in Children and Adolescents With Mania Associated With Bipolar I Disorder: A 3-Week, Double-Blind, Placebo-Controlled Trial

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Supplementary eAppendix 1. The Trial 149 Study Investigators

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Supplementary eAppendix 2. Details of the safety analyses

Categorical worsening in Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS) scores was investigated using generalized estimating equation (GEE) analysis. GEE analysis was used as assumptions of normality did not hold for SAS and AIMS total scores or the BARS global score. Covariates included age stratum, treatment, visit, visit-by-treatment interaction, and baseline score. ANCOVA was used to assess change from baseline to Day 21 in prolactin concentration over time. Rates of anticholinergic medication use in the quetiapine and placebo groups were compared using logistic regression. Suicidality analyses were conducted post hoc utilizing standardized classifications similar to those in the Columbia Suicidality Classification Project.[1] Remaining safety analyses used descriptive statistics.

REFERENCE

1. Posner K, Oquendo MA, Gould M, et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007;164(7):1035–1043.

Supplementary eTable 1. Key Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Age 10 to 17 years • Male or female • BP-I mania (DSM-IV-TR, confirmed by K-SADS-PL) • YMRS total score ≥ 20 at screening and randomization • Confirmed absence of pregnancy	• DSM-IV diagnosis of Axis I disorder other than bipolar I disorder or ADHD • Premorbid intelligence quotient <70 or diagnosis of mental retardation • History of serious suicide attempt, at current suicide risk, or at serious homicide risk • Psychotic symptoms related to medication or substance abuse or judged to be direct physiological consequence of a medical treatment or condition • Current manic episodes that resulted from psychostimulant or antidepressant medication • TSH concentration more than 10% above the upper limit of the normal range • Laboratory test results outside the normal reference range • Unstable diabetes mellitus with a baseline glycosylated hemoglobin (HbA1c) ≥8.5 • A hospital admission for diabetes or related illness in the past 3 months • Other medical conditions that were unstable or may have affected or been affected by the study medication and pregnancy or lactation • Concurrent cognitive-behavioral therapy initiated within 6 weeks prior to randomization

ADHD, attention deficit hyperactivity disorder; DSM-IV-TR, Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, text revision; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version; TSH, thyroid-stimulating hormone.