A 12-Week Single-Blind Trial of Quetiapine for the Treatment of Mood Symptoms in Adolescents at High Risk for Developing Bipolar I Disorder

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Objective: To investigate the effectiveness and tolerability of quetiapine for the treatment of adolescents at high risk for developing bipolar I disorder.

Method: Twenty adolescents (aged 12–18 years) with mood symptoms that did not meet DSM-IV-TR criteria for bipolar I disorder and who had at least one first-degree relative with bipolar I disorder were recruited from August 2003 to June 2005 to participate in a single-blind, 12-week prospective study of quetiapine. Subjects were diagnosed using the Washington University in St. Louis Kiddie Schedule of Affective Disorders and Schizophrenia and were symptomatic, defined by a Young Mania Rating Scale (YMRS) score ≥ 12 or a Childhood Depression Rating Scale-Revised Version (CDRS-R) score ≥ 28 at baseline. The primary effectiveness measure was an endpoint Clinical Global Impressions-Improvement scale (CGI-I) score ≤ 2 ("much" or "very much" improved). Secondary efficacy measures included change from baseline to endpoint in YMRS and CDRS-R scores.

Results: Mood disorder diagnoses in the adolescents consisted of bipolar disorder not otherwise specified (N = 11), dysthymia (N = 3), bipolar II disorder (N = 3), cyclothymia (N = 2), and major depressive disorder (N = 1). The majority of patients (N = 12, 60%) were non-responders to previous trials of psychotropic agents. Fifteen subjects (75%) completed all study visits. Eighty-seven percent of patients were responders (CGI-I ≤ 2) to quetiapine at week 12 (mean ± SD endpoint dose = 460 ± 88 mg/day). YMRS scores decreased from 18.1 ± 5.5 at baseline to 8.7 ± 7.9 at endpoint ($p < .0001$), and CDRS-R scores decreased from 38.2 ± 9.8 to 27.7 ± 9.3, ($p = .0003$). The most frequently reported adverse events were somnolence, headache, musculoskeletal pain, and dyspepsia. No subjects discontinued study participation due to adverse events.

Conclusion: Although these findings are limited by the small sample size and open-label treatment, the results suggest that quetiapine may be an effective treatment for mood symptoms in adolescents with a familial risk for developing bipolar I disorder.

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Despite the significant morbidity and mortality often associated with bipolar I disorder during adolescence,[1,2] there have been few studies examining early intervention or preventative strategies for this illness. One explanation for this may be that prodromal presentations specific to bipolar I disorder have not yet been validated in prospective studies. Additionally, until recently it was unknown which treatments were effective for adolescents with bipolar I disorder, making it difficult to select evidence-based options for early intervention strategies.[3] Nonetheless, effective treatments for adolescents with risk factors for developing bipolar I disorder could delay the progression to bipolar I disorder and ultimately improve long-term outcome.[3]

Adolescents with a first-degree relative with bipolar I disorder have an elevated risk for developing bipolar I disorder themselves.[4–6] Additionally, adolescent offspring of bipolar parents have an increased risk of other psychiatric disorders, including depression, anxiety, and disruptive behavior disorders, which may be prodromal presentations of incipient bipolar disorder.[4–13] Therefore, one approach to identifying early intervention and ultimately preventive strategies for bipolar disorder is to target children and adolescents with a familial risk for bipolar I disorder but who have not yet developed bipolar I disorder.

Children and adolescents with depressive disorders[6,7] as well as those with bipolar spectrum disorders[14] have an elevated risk for subsequently developing bipolar I disorder. For example, in a recent longitudinal outcome study, Birmaher and colleagues[14] reported that 21% of youth with bipolar II disorder and 20% of youth with bipolar disorder not otherwise specified (NOS) had a manic or mixed episode during follow-up and thus switched to bipolar I disorder. Whether the risk of conversion is related to natural illness progression, misdiagnosis, or precipitation of mania by ineffective interventions for prodromal symptoms of bipolar I disorder (e.g., inattention or depression) remains unclear. Indeed, there are data indicating that stimulants and antidepressants may precipitate or exacerbate manic symptoms and possibly even accelerate the onset of bipolar I disorder,[15–17] emphasizing the importance of establishing safe and effective treatment options for mood symptoms in youth with risk factors for developing bipolar I disorder.

Results from recent controlled studies have demonstrated that atypical antipsychotics are efficacious for improving mood symptoms in adolescents with bipolar I disorder.[18–20] Among the atypical antipsychotics, quetiapine has been shown to reduce the severity of both manic and depressive symptoms in children, adolescents, and adults and is, in general, well tolerated.[19,20]

With these considerations in mind, we examined the use of quetiapine in adolescents at high risk for developing bipolar I disorder. Specifically, we hypothesized that quetiapine would be effective and well tolerated for the treatment of adolescents with mood symptoms in the absence of bipolar I disorder who were at risk for this condition due to having a first-degree relative with bipolar I disorder. To our knowledge, this is the first investigation evaluating an atypical antipsychotic for this patient population.

METHOD

This study was a 12-week prospective investigation of the effectiveness and tolerability of quetiapine for the treatment of mood symptoms in adolescents with a mood disorder other than bipolar I disorder and a first-degree relative with bipolar I disorder. The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Cincinnati (Cincinnati, Ohio) Institutional Review Board. All study participants were fluent in English, agreed to participate in the study, provided written assent, and had a legal guardian who also provided written consent prior to study-related procedures.

Subjects

Adolescents (aged 12–18 years) with a mood disorder other than bipolar I disorder and at least one first-degree relative (parent or sibling) with bipolar I disorder were recruited from August 2003 to June 2005 through community referrals. Parental diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID-P)[21] administered by trained raters ($\kappa > 0.9$). All potential study participants were evaluated using the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-K-SADS),[22] which was administered by trained interviewers with established symptom and diagnostic reliabilities ($\kappa > 0.9$).[2,11] The adolescents and their primary caregivers were interviewed separately, and their responses were combined to ascertain diagnoses. All diagnoses were reviewed in a consensus conference attended by at least 1 child and adolescent psychiatrist.

Adolescents were included in the study if they were diagnosed with at least one of the following: bipolar II disorder, bipolar disorder NOS, cyclothymia, major depressive disorder, dysthymia, or depressive disorder NOS, according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) criteria. Bipolar Disorder NOS was diagnosed in individuals who were missing 1 criterion or had all criteria but did not meet duration for a DSM-IV-TR–defined manic episode. Additionally, adolescents were included only if they had a baseline Young Mania Rating Scale (YMRS)[23,24] score ≥ 12 or a Children's Depression Rating Scale-Revised Version (CDRS-R)[25] score ≥ 28. Adolescents were excluded from study participation if they were pregnant or lactating, required hospitalization for a psychiatric disorder, had a substance use (other than nicotine use) disorder within the previous 3 months or an unstable medical or neurologic illness as determined by a study physician, had active suicidal ideation at screening or baseline, or had a history of intolerance or nonresponse to quetiapine.

Study Procedures

Treatment was performed on an outpatient basis. After a washout period of 28 days for fluoxetine, 7 days for antidepressants, anticonvulsants, antipsychotics, or atomoxetine, and 48 hours for psychostimulants, quetiapine was administered. Quetiapine was initiated at a dose of 100 mg/day on day 1 and titrated to 400 mg/day by day 4. The target dose range for quetiapine was flexible within 300 and 600 mg/day. The study physician made dosage adjustments within this range on the basis of effectiveness and tolerability assessments. Quetiapine was administered once daily, between 5:00 and 7:00 p.m. No concomitant psychotropic medications were permitted during the study. Subjects who had been treated with psychotherapy for at least 3 months prior to study participation were allowed to continue. However, subjects were not allowed to begin psychotherapy during study participation.

Adherence was measured by pill count at each visit as well as by asking each study participant to keep a medication log to encourage adherence and identify missed doses. Subjects were discontinued from the study if they missed more than 2 consecutive days of study medication or more than 3 doses during any 7-day period.

Study participants were assessed weekly for 4 weeks and then every 2 weeks until week 12 (days 0, 7, 14, 21, 28, 42, 56, 70, and 84). All effectiveness and tolerability ratings were performed at each visit by trained raters with established reliabilities ($\kappa > 0.9$) for all scales. Raters who performed effectiveness ratings were not informed of the study treatment and aims nor of the tolerability ratings and adverse events of study participants.

Effectiveness Measures

The primary effectiveness measure was percent responders, defined by an endpoint Clinical Global Impressions-Improvement scale (CGI-I)[26] score ≤ 2 ("much" or "very much" improved). Secondary effectiveness measures included changes in YMRS and CDRS-R scores from baseline to endpoint. The Children's Global Assessment Scale (CGAS)[27] was administered at baseline and endpoint. All effectiveness ratings were based on the combined responses from patients and their caregivers.

Tolerability and Safety Assessments

Tolerability and safety assessments included reports of adverse events, measurements of vital signs, laboratory tests, and movement scales to evaluate extrapyramidal symptoms (EPS). Reports of adverse events were based on responses by patients and caregivers to open-ended questions about potential side effects. Vital sign evaluations included body mass index, which was calculated from weight and height measurements, as well as orthostatic blood pressure and pulse. The Simpson-Angus Scale,[28] Barnes Akathisia Scale,[29] and Abnormal Involuntary Movement Scale[30] were used to assess EPS.

Electrocardiograms (ECGs) and laboratory tests, including complete blood cell counts and liver function tests (alanine aminotransferase, aspartate aminotransferase, and total bilirubin) as well as tests to determine prolactin, thyroid-stimulating hormone, electrolyte, and glucose levels were performed at baseline and endpoint.

Statistical Analyses

Statistical analyses were performed using Statistical Analysis System (SAS) software for the personal computer (SAS Institute, Cary, N.C.). Effectiveness and tolerability assessments were performed on the intent-to-treat (ITT) population, which included all patients who received at least 1 dose of study medication (N = 20). Repeated-measures analyses of variance (ANOVAs), accounting for within-subject variance and using last-observation-carried-forward (LOCF) data, were used to examine changes in YMRS and CDRS-R scores over time (PROC MIXED). A paired t test was used to examine changes in YMRS, CDRS-R, and CGAS scores from baseline to endpoint. Nonparametric Fisher exact and Wilcoxon tests were used to compare demographic and clinical variables that were categorical and continuous, respectively, between CGI-I responders and nonresponders. Paired t tests were also used to compare group differences in change from baseline to endpoint in safety and laboratory measures. Rates of adverse events were calculated and tabulated. Descriptive data are presented in means (SD) or number of subjects (percentage of total subjects). Other analyses were performed as needed.

Table 1. Demographic and Clinical Variables for 20 Adolescents With a Mood Disorder Other Than Bipolar I Disorder and a First-Degree Relative With Bipolar I Disorder[a]

Variable	Study Participants (N = 20)
Age, mean (SD)	14.7 (1.7)
Female	8 (40)
White	18 (90)
Affective disorder diagnosis	
Bipolar disorder NOS	11 (55)
Bipolar II disorder	3 (15)
Dysthymia	3 (15)
Cyclothymia	2 (10)
Major depressive disorder	1 (5)
Co-occurring diagnoses	
Attention-deficit/hyperactivity disorder	7 (35)
Oppositional defiant disorder	5 (25)
Conduct disorder	3 (15)
Anxiety disorders[b]	3 (15)

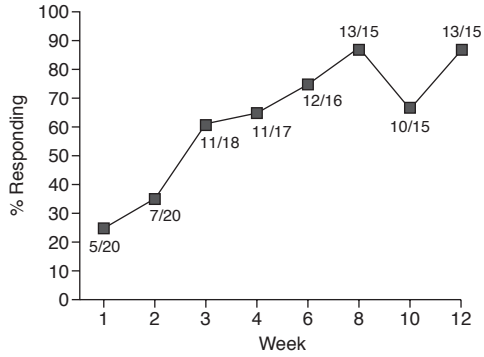
[a]All values shown as N (%) unless otherwise noted.
[b]Anxiety disorders included 1 subject each with separation anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder.
Abbreviation: NOS = not otherwise specified.

RESULTS

Study Participant Characteristics

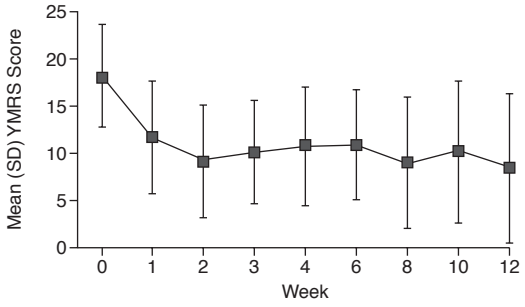
Thirty-one adolescents with a first-degree relative with bipolar I disorder were screened for potential study participation. However, 11 adolescents did not meet study inclusion criteria (7 did not meet mood disorder inclusion criteria, 1 had an active substance use disorder, 1 was pregnant at screening, 1 refused medication, and 1 was lost to follow-up prior to baseline). Demographic and clinical characteristics, including mood disorder diagnoses of the 20 study participants, are listed in Table 1. The majority of study participants (N = 12, 60%) reported no improvement or worsening of symptoms in previous trials of psychotropic agents. Specifically, 8 patients (40%) reported unsuccessful prior antidepressant trials, 6 (30%) had prior psychostimulant trials, and 2 (10%) had prior treatment with antiepileptic agents (1 each with divalproex and oxcarbazepine). Three patients (15%) reported previous trials of both antidepressants and psychostimulants, and 3 (15%)

Figure 1. Proportion of Study Participants Responding (defined by a CGI-I score ≤ 2) to Treatment With Quetiapine Over the 12 Weeks of the Study



Abbreviation: CGI-I = Clinical Global Impressions-Improvement scale.

Figure 2. Change in Mean (SD) YMRS Score (LOCF data) Over 12 Weeks of Treatment With Quetiapine in Adolescents With a Mood Disorder Other Than Bipolar I Disorder and a First-Degree Relative With Bipolar I Disorder[a]



[a]Repeated-measures analysis of variance revealed a statistically significant decrease in YMRS scores over time (F = 4.6, df = 8,152; p = .0002).
Abbreviations: LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

had more than one trial with attention-deficit/hyperactivity disorder (ADHD) medications.

Eleven study participants (55%) had a male (father N = 10, brother N = 1) first-degree relative with bipolar I disorder, whereas 6 (30%) had a female (mother N = 5, sister N = 1) first-degree relative and 3 (15%) had both parents with bipolar I disorder.

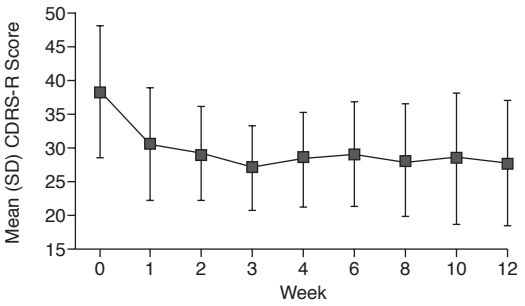
Fifteen subjects (75%) completed the 12-week treatment period. Reasons for discontinuation included lack of efficacy (N = 2, days 14 and 42), nonadherence (N = 2, days 28 and 42), and withdrawal of consent (N = 1, day 14). The mean (SD) quetiapine endpoint dose was 460 (88) mg/day, with a range of 400 to 600 mg/day.

Effectiveness Ratings

The percentage of patients who responded, defined by a CGI-I score ≤ 2, increased from 25% at week 1 to 87% at week 12 (Figure 1). There were no statistically significant differences between responders and nonresponders in age, sex, sex of first-degree relative with bipolar disorder, prior medications trials, co-occurring ADHD, or co-occurring disruptive behavior disorders (conduct disorder or oppositional defiant disorder) (all $p > 0.3$). Overall, 15 (75%) of the 20 study participants responded during the study. Three (27%) of the 11 adolescents with bipolar disorder NOS were nonresponders, the adolescent with MDD was a nonresponder, and 1 (50%) of the 2 adolescents with cyclothymia was a nonresponder.

Repeated-measures ANOVA revealed a statistically significant decrease in YMRS score over time (F = 4.6, df = 8,152; $p < .0001$) (Figure 2). Specifically, mean (SD) YMRS score decreased from 18.1 (5.5) at baseline to 8.7 (7.9) at endpoint ($t = –4.4$, df = 152, $p < .0001$). There was also a statistically significant decrease in CDRS-R score over time (F = 4.0, df = 8,152; p = .0002) (Figure 3).

Figure 3. Change in Mean (SD) CDRS-R Score (LOCF data) Over 12 Weeks of Treatment With Quetiapine in Adolescents With a Mood Disorder Other Than Bipolar I Disorder and a First-Degree Relative With Bipolar I Disorder[a]



[a]Repeated-measures analysis of variance revealed a statistically significant decrease in CDRS-R scores over time (F = 4.0, df = 8,152; p = .0002).
Abbreviations: CDRS-R = Childhood Depression Rating Scale-Revised Version, LOCF = last observation carried forward.

Specifically, mean (SD) CDRS-R score decreased from 38.2 (9.8) at baseline to 27.7 (9.3) at endpoint ($t = –3.7$, df = 152, $p < .001$). Mean (SD) CGAS score increased from 45 (8) at baseline to 64 (13) at endpoint (t = 19.3, df = 19, p = .0003).

Tolerability

The most commonly reported adverse events during the study were somnolence, headache, musculoskeletal pain, and dyspepsia (Table 2). Adverse events were rated mild or moderate and were not associated with study discontinuations. No serious adverse events occurred during the study.

Table 2. Commonly (≥ 10% of participants) Reported Adverse Events in Adolescents (N = 20) at Risk for Developing Bipolar Disorder During 12 Weeks of Treatment With Quetiapine

Adverse Event	N (%)
General	
Headache	5 (25)
Musculoskeletal pain	5 (25)
Nervous system	
Somnolence	11 (55)
Tremors	3 (15)
Digestive	
Dyspepsia	5 (25)
Vomiting	2 (10)
Respiratory	
Congestion	3 (15)

The mean (SD) body weight of participants increased from 62.6 (16.0) kg at baseline to 66.4 (16.4) kg at endpoint ($t = 5.3$, $df = 19$, $p < .0001$). Body mass index increased from 23.0 (5.1) kg/m^2 at baseline to 24.4 (5.5) kg/m^2 at endpoint ($t = 4.9$, $df = 19$, $p < .0001$). No statistically or clinically significant changes were observed in any of the laboratory or EPS measures. There were no clinically significant changes in vital signs or ECG measures. Specifically, there were no incidences of orthostatic hypotension or corrected QT (QTc) interval prolongation (> 450 msec). QTc interval decreased from 409 (16) msec at baseline to 404 (15) msec at endpoint ($t = –1.2$, $df = 19$, $p = .2$).

DISCUSSION

The results of this study indicated that most of the patients exhibited significant improvement in mood symptoms following treatment with quetiapine. In general, response rate steadily increased throughout the 12 weeks of treatment. Moreover, study participants exhibited reductions in symptoms of mania and depression, as well as improvement in overall functioning, as measured by the YMRS, CDRS-R, and CGAS, respectively. Decreases in symptoms of mania and depression were observed as early as the initial postbaseline assessment at week 1 and were maintained until the end of the study at week 12.

In general, the findings of this study also suggest that quetiapine was well tolerated. Although sedation and weight gain were common, these adverse effects did not result in study discontinuation and are consistent with those reported in prior studies of adolescents treated with quetiapine.[19,20] Future studies that examine the effects of quetiapine on lipid levels and glucose regulation in children and adolescents are needed.

This study serves as an initial step in examining whether treatment with quetiapine is an effective early intervention, and ultimately a preventative strategy, for adolescents with incipient bipolar I disorder. Although prospective longitudinal studies are needed to more definitively identify prodromal presentations of bipolar I disorder, our sample consisted of adolescents with 2 established risk factors for developing bipolar I disorder—having a first-degree family member with bipolar I disorder and having an early-onset mood disorder other than bipolar I disorder—suggesting that the study participants very likely had symptoms of prodromal bipolar I disorder. However, the specificity of these risk factors for predicting the development of bipolar I disorder in a given individual is unknown. Nonetheless, all of the adolescents in our study had active mood symptoms, indicating the need for intervention.

Most of the study participants failed prior treatment trials with antidepressants or psychostimulants. Although controversial, recent data suggest that these medications may accelerate the onset of bipolar I disorder. One proposed mechanism by which this may occur is behavioral sensitization, that is, in which antidepressant and stimulant exposure over time might lead to a progression or worsening of mood symptoms in those who have the genetic risk for developing bipolar disorder.[12] Consistent with this model, prior studies suggest a worsening or earlier onset of mania in youth with exposure to antidepressants or stimulants.[2,12,15–17,31] Therefore, alternative treatment strategies for adolescents at familial risk for bipolar disorder are necessary.

There have been several recent efforts to examine the use of mood stabilizers for adolescents at high risk for developing bipolar disorder. However, variability among the studies in sample characteristics and primary outcome measures make the findings difficult to interpret. For example, Geller and colleagues[32] reported that lithium was no more effective than placebo in a sample of 30 prepubescent youth with major depressive disorder (MDD) and a first- or second-degree relative with bipolar I disorder or a multigenerational/loaded MDD family history. In that study changes in CGAS and mean 9-item-K-SADS scores were used as the main outcome measures. More recently, studies have evaluated valproic acid for at-risk bipolar youth. Specifically, Chang and colleagues[33] found that open-label divalproex treatment provided a 78% response rate, as defined by a CGI-I score ≤ 2, in children and adolescents with a current or past diagnosis of ADHD, cyclothymia, dysthymia, or major depressive disorder and at least one parent with bipolar I or II disorder. In contrast, Findling and colleagues[34] report that divalproex was no more effective than placebo for the treatment of children and adolescents with cyclothymia or bipolar disorder NOS and a parent with a bipolar disorder. Primary outcome measures were time to treatment discontinuation for any reason and treatment discontinuation due to a mood event. Overall, because of the methodological differences among these studies, it is difficult to formulate conclusions based on the existing literature.

Until recently, there were few systematic pharmacologic intervention studies of bipolar youth to guide the choice of which treatments might be effective for children and adolescents at risk for developing bipolar disorder.[3] Despite the well-established positive treatment effects of mood stabilizers, such as divalproex and lithium, for bipolar adults, recent studies reported that these agents may be less effective for children and adolescents with bipolar disorder than previously believed.[35,36] In contrast, results from controlled investigations indicated that atypical antipsychotics are useful for the treatment of adolescents with bipolar disorder, suggesting that these medications may produce a favorable response in at-risk youth.[18–20] Indeed, although placebo-controlled studies are needed to confirm the findings, the results of this study suggest that quetiapine is effective and well tolerated for the treatment of mood symptoms in a sample of adolescents who are at risk for developing bipolar I disorder. By reducing the severity of prodromal symptoms, it may be possible to attenuate the progression to bipolar I disorder in a proportion of these adolescent patients.

Limitations

Several limitations should be considered when interpreting the results of this study. First, the sample size was small and there were few nonresponders, making it difficult to determine predictors of response. Second, since most of the adolescents in this study had been already diagnosed with a bipolar spectrum disorder (bipolar II disorder, bipolar disorder NOS, or cyclothymia), they might no longer be considered "high risk." Future studies examining the long-term effects of early interventions in children and adolescents with a bipolar parent, prior to the onset of a bipolar spectrum or other mood disorder, are needed to establish preventative strategies. Third, although the majority of study participants were diagnosed with bipolar disorder NOS, the sample consisted of adolescents with heterogeneous diagnoses. We observed significant reductions in YMRS and CDRS-R scores within the entire sample. However, because of the small sample size and variability in diagnoses among study participants, we were unable to examine symptom changes within specific diagnostic categories. A larger sample size or a sample of adolescents at familial risk for bipolar disorder with a single diagnosis (e.g., bipolar disorder NOS) would permit such analyses. Additionally, although most of the adolescents had at least one parent with bipolar disorder, 2 of the subjects had a sibling with bipolar disorder, which may have added environmental and genetic heterogeneity to the sample. Fourth, the design of this study was open-label, and therefore the placebo effect of study participation is unknown. However, this study was rater-blinded in an effort to minimize the potential for outcome rating biases. Specifically, raters who performed symptom ratings were not informed of the study design or aims. Finally, the study duration was only 12 weeks, which is insufficient to characterize the long-term effectiveness and tolerability of quetiapine for this population. Moreover, because of the short study duration and the lack of a control group, whether quetiapine is effective as an early intervention or preventative treatment for bipolar I disorder in those at risk remains an area for future investigation.

Nonetheless, the results of this study provide initial support for quetiapine as a treatment for mood symptoms in adolescents at high risk for developing bipolar I disorder. On the basis of these findings, future double-blind placebo-controlled trials that include a larger sample size and are of longer duration are warranted to examine the efficacy of quetiapine as an early intervention for bipolar I disorder.

Drug names: atomoxetine (Strattera), divalproex (Depakote), fluoxetine (Prozac and others), oxcarbazepine (Trileptal), quetiapine (Seroquel), valproic acid (Depakene and others).

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Melissa P. DelBello, M.D., at delbelmp@email.uc.edu.