

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

### **Background:**

- Quetiapine is FDA approved in adults for treating manic symptoms associated with type I bipolar disorder, and evidence has shown that atypical anti-psychotics may have a role in therapy for children and adolescents.
- Quetiapine has been shown to be as effective as divalproex monotherapy and the combination of the two medications was more effective than divalproex alone for treatment of acute bipolar mania in adolescents.

### **Objective:**

- Determine the safety and efficacy of quetiapine 400 mg/d and 600 mg/d versus placebo in children and adolescents with manic symptoms associated with type I bipolar disorder.

### **Methods:**

- **Design:** double blind, randomized, placebo-controlled, parallel group study; **Duration:** 3 weeks
- **Inclusion criteria:** ages 10 to 17, bipolar type I mania based upon DSM-IV criteria, confirmed by K-SADS-PL, YMRS total score  $\geq 20$  at screening and randomization, and not pregnant
- **Exclusion criteria:** DSM-IV diagnosis of axis I disorder other than bipolar I or ADHD, premorbid intelligence quotient  $< 70$  or diagnosis of mental retardation, serious suicide attempt, current suicide or homicide risk, psychotic symptoms related to medication or substance abuse, current manic episodes resulting from psychostimulant or anti-depressants, TSH concentration more than 10% above normal range, lab test results outside normal reference range, unstable diabetes mellitus, hospital admission for diabetes or related illness within past 3 months, other unstable medical conditions, concurrent cognitive-behavioral therapy initiated within 6 weeks of randomization
- **Patients enrolled:** 284 total; quetiapine 400mg/d = 95; quetiapine 600mg/d =98; placebo = 91
- **Drug regimens/dosages used:** Quetiapine groups started on 50 mg on day 1, 100 mg on day 2, and increased by 100 mg/day until day 5 with the 400 mg/day group and until day 7 in the quetiapine 600 mg/day group. Two to three divided daily doses were given based on tolerability.
- **Primary Outcome Measure:** Evaluation of mean change from baseline to day 21 in YMRS total score.
- **Secondary Outcome Measures:** Proportions of patients achieving criteria for response and remission at day 21, changes in Children's Depression Rating Scale-Revised, Clinical Global Impressions-Bipolar Version Severity of Illness and Global Improvements score, Children's Global Assessment Scale, and Overt Aggression Scale-Modified scores. Patient reported outcomes included change on the Caregiver Strain Questionnaire. Incidents of treatment-emergent depression, clinical and laboratory safety data, emergence of extrapyramidal symptoms, adverse events, weight and vital signs were all reported.
- **Power:** 85% to detect a difference of 6 points in YMRS
- **Data handling method:** intent to treat

### **Results:**

- **Total patients completed**=222; quetiapine 400mg/d=76; quetiapine 600mg/d=80; placebo=66
- **Primary Outcome Measure:** quetiapine 400mg/d and 600 mg/d was associated with significantly greater improvements than placebo in YMRS total score compared to baseline. Mixed model repeated measures analysis was -14.25 (SE=0.96; 95% CI, -16.15 to -12.35) with quetiapine 400mg/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<0.001 each quetiapine dose vs. placebo).

- **Secondary Outcome Measures:** Quetiapine was associated with significantly greater remission rates than placebo and significant improvements in CGI-BP Severity of Illness score vs. placebo (p=0.005 and p<0.001), respectively. Results were also statistically significant for achieving “very much improved” or “much improved” compared to baseline for CGI-BP Global Improvement. Changes in CGAS total score were statistically significant in both quetiapine treatment groups (p<0.05 and p<0.001), respectively. Differences in the Overt Aggression Scale and Caregiver Strain questionnaire were not statistically significant. Adverse effects were reported more frequently in quetiapine groups than placebo, and most commonly included somnolence, sedation, dizziness, and headache. The most frequently reported serious adverse event was exacerbation of bipolar disorder. Mean changes from baseline to final visit in pulse rate, ALT/AST, fasting glucose, total and LDL cholesterol, triglycerides, TSH, and prolactin levels were greater in the quetiapine groups than placebo, although no p-values were reported.
- **Author’s conclusion:** Quetiapine 400 mg/d or 600 mg/d were effective and well tolerated in children and adolescents for manic symptoms associated with type I bipolar disorder.

#### **Strengths:**

- Stratification by age allowed comparisons between ages 10-12 and 13-17
- Patients with co-morbid ADHD were included
- Bipolar disorder is commonly diagnosed at the age included in patient population

#### **Limitations:**

- Other types of bipolar disorder and co-morbid psychological disorders were excluded.
- Short study duration
- Unblinding was likely due to the adverse effect profile of quetiapine.
- Non-flexible dosing protocol was used
- Many factors left up to investigators’ discretion, including washout period, daily dosing schedule, and the relation of adverse effects to study medication.

#### **Conclusion:**

- Quetiapine was effective compared to placebo in adolescents and children; however, it is not without risk. The potential long-term risks are unclear due to the short study duration. Quetiapine should be used cautiously in children, especially those ages 10-12. Children should be closely monitored for adverse effects including exacerbation of bipolar illness, suicide behavior, and unfavorable metabolic effects.
- Studies are needed to evaluate the long term efficacy and safety of quetiapine in adolescents and children with bipolar type I disorder, and in children with other types of bipolar disorder or with other co-morbid psychological disorders.

#### **Reference:**

Pathak S, Findling RL, Earley WR, Acevedo LD, Stankowski J, DelBello MP. Efficacy and Safety of Quetiapine in Children and Adolescents With Mania Associated With Bipolar I Disorder: A 3-Week, Double Blind, Placebo-Controlled Trial. J Clin Psychiatry. 2013; 74(1):100-9.

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