

# RISPERIDONE FOR THE TREATMENT OF ADHD IN CHILDREN WITH BIPOLAR DISORDER

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## Updated Abstract

**Objective.** Children and adolescents with bipolar disorder are also at high risk of having comorbid attention-deficit hyperactivity disorder. The objective of this study to estimate improvement in ADHD symptoms in children enrolled in a clinical trial of risperidone for the treatment of pediatric bipolar disorder. **Methods.** This was an open-label, eight-week study of risperidone monotherapy in the treatment of youth with mania. **Results.** Twenty-nine subjects were assigned to treatment with risperidone for pediatric bipolar disorder. Subjects were 9.9±2.5 years of age and predominantly male (69%). Over the 8 weeks of treatment, there were significant reductions in symptoms of bipolar disorder (change score=-17.9±9.7, p<0.001) and ADHD (-16.4±9.3, p<0.001). Both hyperactive/impulsive (-8.3±4.9, p<0.001) and inattentive (-7.6±4.8, p<0.001) symptoms were improved with risperidone. However, the mean ADHD rating scale score at endpoint was 20.4±9.1 indicating residual ADHD symptomatology. **Conclusions.** This study suggests that risperidone is associated with improvement of both inattentive and hyperactive/impulsive symptoms of ADHD in children with bipolar disorder. However, at endpoint subjects continued to report residual symptoms of the disorder and the majority were not rated as having experienced clinical improvement. Long-term data are required to fully understand the efficacy of risperidone for ADHD symptoms and to estimate functional improvements associated with this level of ADHD improvement

## Introduction

Childhood bipolar disorder is among the most severely disabling psychiatric conditions affecting children. It is associated with great severity of the illness (eg, psychosis, mixed mania, and high rates of aggression) and impairment. Children and adolescents with bipolar disorder are also at high risk of having comorbid attention-deficit hyperactivity disorder (ADHD).

Risperidone has been investigated as a treatment for disruptive behavior disorders and for pediatric bipolar disorder. In randomized clinical trials, risperidone has been shown to independently improve symptoms of conduct and affective disorders. The objective of this study to estimate improvement in ADHD symptoms in children enrolled in a clinical trial of risperidone for the treatment of pediatric bipolar disorder.

Based upon the literature examining risperidone in the treatment of other disruptive behavior disorders and our prior clinical studies of the treatment of pediatric bipolar disorder, we hypothesized that ADHD symptoms would respond to risperidone but that this response would require prior mood stabilization.

## Methods

Subjects were enrolled in an 8-week, open-label monotherapy trial of risperidone. All study procedures were reviewed and approved by the Institutional Review Board. All subjects' parents or guardians signed written informed consent forms and all children signed written assent forms.

Risperidone was initiated at an open-label dose of 0.25mg/day for children ≤ 12 years and 0.5mg/day for older youth to be increased weekly according to response and tolerability to a maximum dose of 2.0mg/day for ≤12 and up to 4 mg/day for older youth. Concomitant psychostimulants were allowed during the study if, in the clinician's judgment, it was in the best interest of the patients to continue this treatment or if the patient did not wish to stop stimulant treatment and only if the patient had been on a stable dose for at least 30 days. Four subjects were also receiving stimulant therapy throughout the trial.

Male or female subjects, 6-17 years of age were included in the trial. Each subject met criteria for DSM-IV bipolar I disorder, DSM-IV bipolar II disorder or bipolar disorder NOS and were currently displaying manic, hypomanic, or mixed symptoms (with or without psychotic features) according to the DSM-IV based on clinical assessment by board certified child and adolescent psychiatrist. Bipolar disorder NOS was defined as either 1) having severe mood disturbance, which meets DSM-IV Criteria A for bipolar disorder but fewer elements in criteria B (only require 2 items for elation category and 3 for irritability), or 2) having a severe mood disturbance lasting at least 4 days (rather than 1 week) but the full diagnostic requirement of the B criteria.

Severity of symptoms were assessed with standardized rating scales for mania (Young Mania Rating Scale; YMRS) and the ADHD rating Scale (ADHD-RS). To assess clinically significant severity and improvement relative to baseline, we used the NIMH Clinical Global Impression (CGI) severity (CGI-S), and improvement (CGI-I) scales rated separately for ADHD and bipolar disorder by study clinicians.

All analyses were intention to treat (ITT) with the last observation (LOC) carried forward for subjects that do not complete the full 8-week study schedule.

## Results

Twenty-nine subjects were enrolled in the trial. 69% were male and the average ages was 9.9±2.7 years. At study endpoint, mean risperidone dose was 1.4±0.7 mg/day. At baseline subjects were markedly impaired according to the YMRS (28.8±8.9) and the ADHD rating scale (37.1±9.7). With regard to manic symptoms, response was robust. The YMRS was reduced by -17.9±9.7 (p<0.001) over 8 weeks with 27 of 29 subjects being considered responders (CGI much or very much improved or a 30% reduction in YMRS score). Response was rapid with 17 (58%) responding within 3 weeks.

Figure 1 illustrates the mean ADHD-RS at each point assessed. There was a statistically significant reduction in symptoms at both week 4 and week 8. Stratification by ADHD symptom subtype and the rate of response of manic symptoms is presented in Figures 2 and 3.

Figure 1. ADHD Response

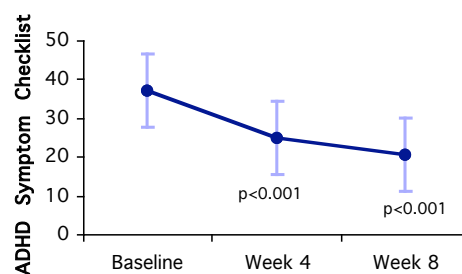


Figure 2. Inattention-IA

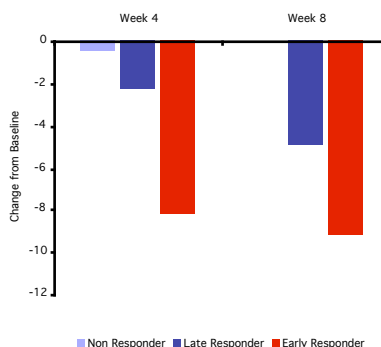
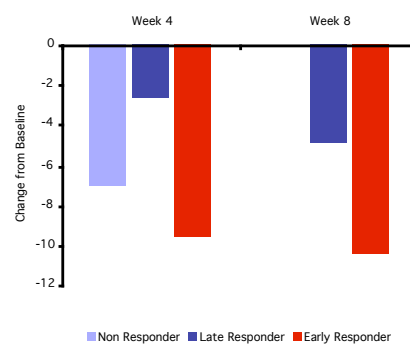


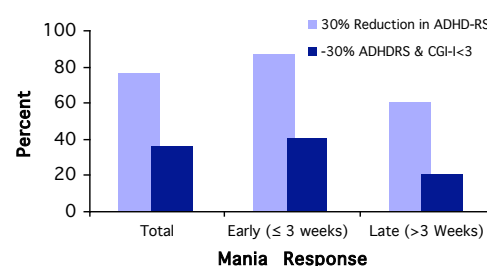
Figure 3. Hyperactive/Impulsive-HI



For both Hyperactive/Impulsive and Inattentive symptoms, there was significant improvement in both groups of mania responders relative to the non responders (p<0.01 each). Furthermore, the pattern of ADHD response was different for both symptom groups in early and late mania responders indicating that ADHD response at week 4 was significantly greater in those that had already registered a mania response (p=0.003 for IA and p=0.003 for HI symptoms). Statistical adjustment for concomitant stimulant therapy did not effect the pattern or the statistical significance of the results.

Categorical measures of ADHD response at endpoint are presented in Figure 4. Despite the high proportion of subjects with a 30% reduction of ADHD symptoms, a much smaller proportion of subjects were also considered improved by clinical assessment (CGI rating of Much or Very Much Improved).

Figure 4. ADHD Response



## Conclusion

This pilot open-label study suggests that risperidone is associated with improvement of ADHD symptoms in children with bipolar disorder. These results suggest that prior mood stabilization is necessary for ADHD symptoms to improve. However, both inattentive and hyperactive/impulsive symptoms were improved indicating that risperidone may exert its effects in all symptoms of ADHD. Thus, improvement in ADHD symptoms was not limited to externalizing symptoms such as impulsivity, hyperactivity or agitation.

However, at endpoint subjects continued to report residual symptoms of the ADHD and the majority were not rated as having experienced clinical improvement. Long-term data are required to fully understand the efficacy of risperidone for ADHD symptoms and to estimate functional improvements associated with this level of ADHD improvement.