

Open-Label, 8-Week Trial of Olanzapine and Risperidone for the Treatment of Bipolar Disorder in Preschool-Age Children

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Background: To evaluate short-term safety and efficacy of atypical antipsychotics in a single-site, prospective, open-label, 8-week study of risperidone and olanzapine monotherapy in preschoolers with bipolar disorder (BPD).

Methods: Risperidone was initiated at an open-label dose of .25 mg/day, increased weekly according to response and tolerability to a maximum dose of 2.0 mg/day. Olanzapine was initiated at 1.25 mg/day and increased to no more than 10 mg/day.

Results: Thirty-one children aged 4–6 years were treated with olanzapine ($n = 15$, 6.3 ± 2.3 mg/day) or risperidone ($n = 16$, $1.4 \pm .5$ mg/day). At study end point (week 8 or last observation carried forward), there was a 18.3 ± 11.9 point ($t = -5.6$, $p < .001$) reduction in risperidone-treated subjects and a 12.1 ± 10.4 point ($t = -4.4$, $p < .001$) reduction in Young Mania Rating Scale (YMRS) scores in olanzapine-treated subjects that did not differ between groups ($t = 1.4$, $p = .2$). Response criteria (Clinical Global Impression improvement of “Much” or “Very Much” improved or a YMRS change of $\geq 30\%$ or more) indicated no difference in rate of response with risperidone and olanzapine (69% vs. 53%, $\chi^2_{(1)} = .8$, $p = .4$).

Conclusions: This prospective open study suggests that treatment with risperidone or olanzapine may result in a rapid reduction of symptoms of mania in preschool children with BPD. Because of substantial residual symptomatology and adverse effects, however, a pressing need exists to identify additional safe and effective treatments for the management of BPD in this high-risk population.

Key Words: Atypical antipsychotics, bipolar disorder, children, clinical trial

Emerging evidence documents that pediatric bipolar disorder may onset in the preschool years (Wilens et al 2002; Wozniak et al 1995). Despite findings from pharmacoepidemiologic studies showing that psychotropics are widely used in this age group (Zito et al 2000), there is limited information on pharmacologic treatment of preschoolers in general or those with bipolar disorder in particular. This state of affairs calls for more studies evaluating the safety and effectiveness of antimanic agents in preschoolers.

Previous studies have found that atypical antipsychotics are useful in the management of bipolar disorder and may also be useful for children with bipolar disorder. In a prospective, open-label treatment trial of risperidone for the treatment of acute mania in 30 youth (6–17 years of age) with bipolar disorder, we recently documented a clinical response to risperidone monotherapy (Biederman 2005). Seventy percent of subjects were classified as responders using an a priori definition of response (much or very much improved) on the Clinical Global Impression—Improvement scale or by demonstrating a 30% reduction in the Young Mania Rating Scale (YMRS) total score by study end point. Similarly encouraging results were reported by Frazier et al (2001) in an open trial of olanzapine monotherapy. They found that treatment with olanzapine was associated with significant improvements in both the Children’s Depression

Inventory and the Young Mania Rating scale in 23 manic children after 8 weeks of monotherapy. Because these studies excluded preschoolers, however, there is a need to further evaluate whether these compounds are associated with similar improvements in younger children as well.

Identifying safe and efficacious treatments for preschoolers is of high clinical and public health relevance. Clinicians who are called on to treat preschoolers with a severe symptomatic picture highly suggestive of bipolar disorder have almost no evidence available to help base treatment decisions. Considering that the population of children referred for treatment of pediatric bipolar disorder includes very young children of preschool years, the identification of safe and efficacious treatment deployed proximally to the onset of symptoms could result in early stabilization and better outcomes for afflicted children.

The main purpose of this study was to estimate the rate of response associated with risperidone and olanzapine monotherapy in preschoolers with bipolar disorder. To this end, we conducted a pilot, open-label study of 8 weeks in children aged 4 to 6 years. To our knowledge, this study represents one of the few systematic evaluations of therapeutic approaches aimed at preschoolers with bipolar disorder.

Methods and Materials

The study consisted of an 8-week, open-label treatment with risperidone or olanzapine. All study procedures were reviewed and approved by the Partners Human Research Committee, Institutional Review Board, at Massachusetts General Hospital. All subjects’ parents or guardians signed written informed consent forms.

Male or female subjects, aged 4–6 years, were included in the trial. Each subject met criteria for DSM-IV bipolar I disorder, DSM-IV bipolar II disorder, or bipolar disorder not otherwise specified (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 an experienced child and adolescent psychiatrist. The DSM-IV re-

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quires subjects to meet criterion A for a period of extreme and persistently elevated, expansive or irritable mood lasting at least 1 week, plus criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance. Also recorded was the onset of first episode, the number of episodes, offset of last episode, and total duration of illness. 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 two items are required for the elation category and three 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. Of the 31 subjects included here, 27 met criteria for bipolar I disorder and 4 met criteria for bipolar disorder NOS due to episodes that were severely impairing but shorter than 1 week in duration.

Severity of symptoms of mania was assessed with the Young Mania Rating Scale (YMRS; Gracious et al 2002; Young et al 1978; Youngstrom et al 2002). During this baseline evaluation the clinicians completed the YMRS as a measure of current symptom severity. To be included in the study, subjects must have had a score of 15 or greater on the YMRS. To assess the rates of psychiatric comorbidity, structured diagnostic interview Kiddie Schedule of Affective Disorders and Schizophrenia Epidemiological Version (KSADS; Ambrosini 2000) were conducted with mothers. These interviews were administered by highly trained and supervised nonclinician interviewers. All diagnoses were reviewed by a sign-off committee of experienced board-certified child and adolescent psychiatrists chaired by the senior investigator (JB).

We excluded subjects with any serious, unstable medical illness including hepatic, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic disease. No subjects were tapered off current antimanic medications for the purpose of enrolling in this study unless the current treatment was determined to be ineffective as indicated by continuing to meet entrance criteria (active symptoms of mania and a YMRS Score of ≥ 15).

Risperidone was initiated at an open-label dose of .25 mg/day to be increased weekly according to response and tolerability to a maximum dose of 2.0 mg/day. Olanzapine was initiated at an open-label dose of 1.25 mg/day to be increased weekly according to response and tolerability of 10 mg/day. If subjects had never been treated with either medication, they were assigned randomly to one of the treatment arms. Subjects with a history of one of these medicines were assigned to the other arm. Subjects who had a history of treatment with both medications were not eligible for this study.

No other antimanic or mood-stabilizing medications or antidepressants were permitted in the study. If subjects were currently receiving stimulants for comorbid ADHD, they would have been continued only if the patient had been on a stable and effective dose for at least 30 days. Forty percent of subjects reported a history of stimulant exposure, but none of the subjects enrolled in this study were currently being treated with stimulants. If extrapyramidal symptoms occurred, benzotropine mesylate was allowed in doses of up to a maximum of 2 mg/day. The use of the benzodiazepine lorazepam was permitted during the study in doses of 2 mg or less per day. One subject received benzotropine (.25 mg) on week 2 and another subject received lorazepam (.5 mg) on weeks 7 and 8. Both subjects completed the trial. Nonpharmacologic treat-

ments such as individual, family, or group therapy were allowed if they were in place before the subject joined the study and if the therapy regimen remained the same throughout the study. Data on the presence or type of nonpharmacologic intervention was not recorded.

The severity of symptoms of depression were assessed with the Children's Depression Rating Scale—revised (CDRS; Emslie et al 1997). Psychotic symptoms were assessed at baseline and end point with the Brief Psychiatric Rating Scale (BPRS; Lachar et al 2001). We used the approach proposed by Lachar et al (2001) to characterize symptom severity in the BPRS using a modified factor terminology. "Resistance" was renamed Mania Symptoms (Uncooperativeness, Hostility, Excitement, Grandiosity); Positive Symptoms (Unusual Thought Content, Conceptual Disorganization, Hallucinatory Behavior, Suspiciousness, Disorientation) and Negative Symptoms (Blunted Affect, Emotional Withdrawal, Motor Retardation) remained the same; Psychological Discomfort was renamed Anxious/Depressed (Anxiety, Somatic Concerns, Guilt Feelings, Tension, Depressive Mood, Mannerisms and Posturing).

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 (National Institute of Mental Health 1985); CGI severity and improvement were assessed separately for depression, mania, conduct disorder, and ADHD. The score for the CGI-S ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The score for the CGI-I ranges from 1 (very much improved) to 7 (very much worse).

The YMRS and the CGI-I mania scale were the primary outcome measures identified for this study. Response was defined by having either a 30% reduction in symptoms according to the YMRS at end point or by having been judged as much or very much improved on the CGI-Improvement (≤ 2). These ratings were made at each of the weekly assessments. Our secondary measures of outcome (the CDRS and the BPRS) were assessed at baseline, week 4, and week 8 (or study end point). To reflect the degree of symptom resolution, we also defined euthymia as having a YMRS score of < 10 at study end point for symptoms of mania and a CDRS score of ≤ 28 for symptoms of depression (Emslie et al 1997).

Safety was assessed at each visit using spontaneous reports of treatment-emergent adverse effects, changes in vital signs and laboratory measures. Blood pressure and weight were recorded at each visit. Prolactin, glucose, and lipid levels were obtained at baseline and posttreatment. Socioeconomic status was determined by the Hollingshead four-factor measure (Hollingshead 1975).

Statistical Analysis

Random regression models were used to analyze the eight repeated measures of the study utilizing generalized estimating equations as implemented in STATA. All analyses were intention to treat with the last observation carried forward (LOCF) for subjects who did not complete the full 8-week study schedule. Statistical significance was determined at $p < .05$.

Results

Thirty-one subjects were enrolled in the trial ($n = 16$ for risperidone and $n = 15$ for olanzapine). Seventy-seven percent ($n = 24$) of subjects completed the 8-week phase of the study. The rate of dropout was statistically significantly greater for

olanzapine than for risperidone ($n = 6$ [40%] vs. $n = 1$ (6%), respectively; $\chi^2_{(1)} = 5.0, p = .03$). Reasons for dropout included side effects ($n = 1$), lack of efficacy ($n = 4$), and loss to follow-up ($n = 2$).

As shown in Table 1, there were no differences between risperidone- and olanzapine-treated subjects on any demographic or clinical variables. The majority of subjects in both groups presented with mania mixed with depression at study entry (Table 1). At study entry symptoms of ADHD and conduct disorder were common in both groups of subjects. Global assessment of function scores indicate that both groups of children were severely impaired (Table 1). The average dose of risperidone at study end point was $1.4 \pm .5$ mg/day, and the average dose of olanzapine at study end point was 6.3 ± 2.3 mg/day.

As shown in Figure 1, there was a clinically and statistically significant improvement in both the risperidone- and olanzapine-treated subjects. At study end point (week 8 or last observation carried forward), there was a 18.3 ± 11.9 point ($t = -5.6, p < .001$) reduction in risperidone-treated subjects and a 12.1 ± 10.4 point ($t = -4.4, p < .001$) reduction in YMRS scores in olanzapine-treated subjects ($t = 1.4, p = .2$). The response curves illustrated in Figure 1 over the course of the trial were not statistically significantly different for olanzapine and risperidone-treated subjects [$F(8,29) = 1.5, p = .2$]. This pattern of results was not statistically significantly different for subjects meeting criteria for bipolar disorder NOS ($n = 4$) and bipolar I disorder ($n = 27$) comparing YMRS scores at baseline and end point [$F(1,30) = .01, p = .9$].

The rate of improvement according to Clinical Global Impression (CGI-I ≤ 2) of mania was not statistically significantly different in olanzapine and risperidone-treated subjects (Figure 2). We employed an a priori definition of response on manic symptoms of a 30% reduction in YMRS score or being rated as much or very much improved on the CGI. The proportion of subjects with either a 30% reduction (69% vs. 53%, $\chi^2_{(1)} = .8, p = .4$) or 50% reduction (53% vs. 33%, $\chi^2_{(1)} = 1.2, p = .3$) in YMRS scores was not statistically significantly different in risperidone and olanzapine-treated subjects, respectively. When combined with the CGI results, there was no difference in our definition of

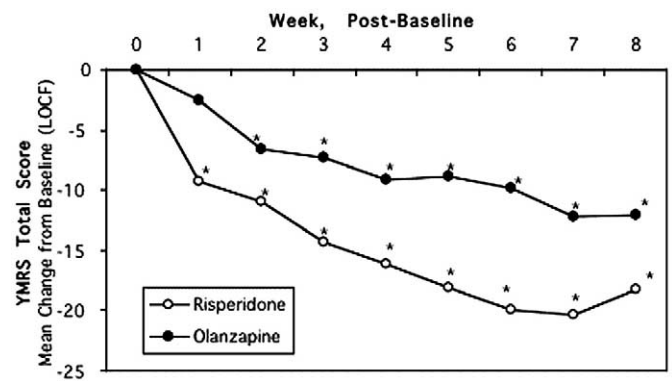


Figure 1. Change in Young Mania Rating Scale Scores (YMRS) in subjects treated with risperidone ($n = 16$) and olanzapine ($n = 15$) in an open study over 8 weeks. * $p < .05$ versus baseline within risperidone and olanzapine arms. LOCF, last observation carried forward.

response in the risperidone and olanzapine-treated subjects (69% vs. 53%, $\chi^2_{(1)} = .03, p = .9$).

The scores from the baseline and end point assessments of the YMRS, CDRS, and BPRS are presented in Table 2. For both the YMRS and the BPRS, there was statistically significant improvement from baseline to end point in both the risperidone- and olanzapine-treated subjects (Table 2). Examination of the individual items of the YMRS revealed that improvement was evident for a wide range of manic symptoms in both study groups. Time-by-treatment interactions indicated that improvement in pressured speech and increased motor activity was statistically significantly greater in risperidone- than in olanzapine-treated subjects. Only subjects treated with risperidone demonstrated a statistically significant improvement in depression as measured by the CDRS (Table 2); however, the time-by-treatment interaction indicated that the putatively greater antidepressant response associated with risperidone was not statistically significantly greater than that for olanzapine.

With the exception of an increase in prolactin levels, analysis of blood work revealed no statistically significant differences from baseline to end point or between olanzapine- and risperidone-treated subjects (Table 3). There was an increase in prolactin in both groups from baseline to end point, but this increase was statistically significantly larger in the risperidone arm. There

Table 1. Demographic and Clinical Characteristics at Baseline

	Risperidone ($n = 16$)	Olanzapine ($n = 15$)	
Demographics			
Age (years)	5.3 ± 0.8	5.0 ± 0.8	$t = -1.0, p = .3$
Gender (% Male)	12 (75%)	10 (67%)	$\chi^2_{(1)} = .3, p = .6$
Ethnicity (% Caucasian)	15 (94%)	15 (100%)	$\chi^2_{(1)} = .9, p = .3$
Socioeconomic status	2.4 ± 1.0	2.4 ± 0.8	$t = .0, p = .9$
Symptoms at Baseline (CGI-S ≥ 3)			
Mania	22 (100%)	17 (100%)	—
Major depression	11 (73%)	11 (73%)	$\chi^2_{(1)} = .0, p = .9$
Conduct disorder	5 (39%)	8 (57%)	$\chi^2_{(1)} = .9, p = .3$
ADHD	14 (93%)	15 (100%)	$\chi^2_{(1)} = 1.0, p = .3$
Past GAF			
Past GAF	44.9 ± 2.8	42.9 ± 4.1	$t = -1.5, p = .2$
Current GAF			
Current GAF	47.3 ± 5.1	45.5 ± 3.6	$t = -1.0, p = .3$
Height (cm)	113.8 ± 6.0	109.8 ± 10.0	$t = -1.3, p = .2$
Weight (kg)	22.4 ± 3.5	20.8 ± 4.8	$t = -1.0, p = .3$

ADHD, attention-deficit/hyperactivity disorder; CGI, Clinical Global Impression; GAF, Global Assessment of Functioning.

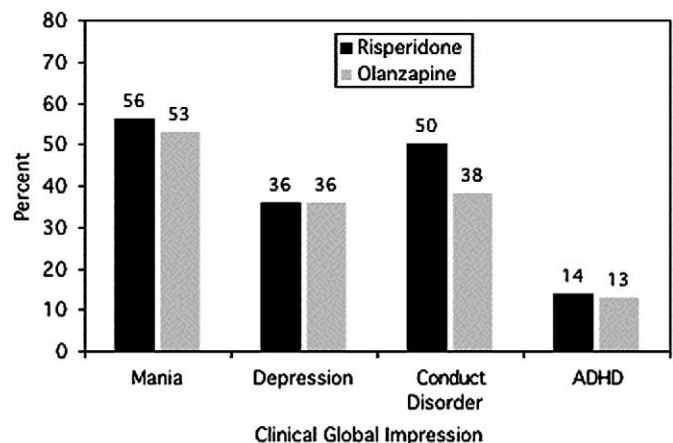


Figure 2. Clinical Global Impression-rated improvement in mania and psychiatric comorbidity. ADHD, attention-deficit/hyperactivity disorder.

Table 2. Rating Scales at Baseline and End Point (Mean \pm SD) in Risperidone or Olanzapine Open Study over 8 Weeks

Scale	Risperidone (n = 16)		Olanzapine (n = 15)		Drug-by-Time Interaction
	Baseline	End Point	Baseline	End Point	
YMRS	35.2 \pm 8.2	16.4 \pm 12.0 ^a	34.2 \pm 6.4	22.1 \pm 8.3 ^a	F(1,30) = 2.01, p = .2
Elated mood	2.8 \pm .8	1.8 \pm 0.9 ^a	2.4 \pm 1.0	1.6 \pm 1.0 ^a	F(1,30) = .2, p = .6
Increased motor activity	3.5 \pm .5	1.8 \pm 1.5 ^a	3.3 \pm .5	2.7 \pm 1.2	F(1,30) = 4.4, p = .04
Sexual interest	2.1 \pm 1.5	.6 \pm 1.1 ^a	1.7 \pm 1.2	.5 \pm .7 ^a	F(1,30) = .1, p = .7
Sleep disturbance	1.9 \pm 1.3	.3 \pm .6 ^a	1.7 \pm 1.2	.3 \pm .6 ^a	F(1,30) = .2, p = .7
Irritability	5.5 \pm 1.5	3.7 \pm 2.0 ^a	5.5 \pm 1.3	4.5 \pm 1.5 ^a	F(1,30) = 1.0, p = .3
Pressured speech	5.1 \pm 1.4	2.7 \pm 2.0 ^a	4.5 \pm 1.9	3.7 \pm 2.1	F(1,30) = 4.6, p = .04
Thought disorder	2.0 \pm .9	.8 \pm .9 ^a	1.9 \pm 1.2	1.2 \pm 1.2	F(1,30) = 1.1, p = .3
Delusional content	3.9 \pm 1.7	1.6 \pm 1.5 ^a	4.0 \pm 2.1	2.3 \pm 1.7 ^a	F(1,30) = .4, p = .5
Aggressive behavior	5.2 \pm 2.0	2.7 \pm 2.4 ^a	5.3 \pm 1.8	3.5 \pm 1.9 ^a	F(1,30) = .4, p = .5
Unkempt appearance	1.1 \pm 1.1	.6 \pm 1.2 ^a	1.6 \pm 1.0	1.0 \pm 1.2 ^a	F(1,30) = .1, p = .7
Lack of insight	2.1 \pm 1.7	.8 \pm 1.4	2.3 \pm 1.2	1.0 \pm 1.2	F(1,30) = 1.97, p = .2
BPRS	46.4 \pm 12.4	33.3 \pm 10.6 ^a	46.7 \pm 13.5	37.8 \pm 11.9 ^a	F(1,30) = .8, p = .4
Resistance (mania symptoms)	18.2 \pm 4.3	11.5 \pm 5.4 ^a	18.4 \pm 2.1	13.7 \pm 5.0 ^a	F(1,30) = .7, p = .4
Positive symptoms	10.0 \pm 3.6	6.6 \pm 2.6 ^a	10.2 \pm 5.9	8.1 \pm 4.0 ^a	F(1,30) < .01, p = .9
Negative symptoms	4.1 \pm 1.8	4.1 \pm 2.1	3.9 \pm 1.6	4.4 \pm 1.6	F(1,30) = .2, p = .6
Psychological discomfort (anxiety/depression)	12.4 \pm 5.3	9.7 \pm 4.0	13.0 \pm 6.7	10.7 \pm 4.2	F(1,30) = .1, p = .9
CDRS	39.7 \pm 10.5	27.0 \pm 6.3 ^a	42.4 \pm 14.8	34.1 \pm 11.5	F(1,30) = .8, p = .4

BPRS, Brief Psychiatric Rating Scale; CDRS, Children's Depression Rating Scale; YMRS, Young Mania Rating Scale.

^ap < .05 versus baseline within risperidone or olanzapine arms.

were no statistically significant changes in measures of cardiac function with the exception of an increase in systolic blood pressure in the risperidone-treated subjects and a small but statistically significant increase in pulse in the olanzapine. There was statistically significant increase in weight from baseline to end point in both risperidone- (2.2 \pm .4 kg) and olanzapine- (3.2 \pm .7 kg) treated subjects (Table 3). This weight increase resulted in an average percentage of body weight increase of 10.1 \pm 6.1% with risperidone and of 12.9 \pm 7.1% with olanzapine.

As illustrated in Figure 3, the rate of spontaneously reported side effects did not differ between risperidone- and olanzapine-treated subjects. In both groups, the most commonly reported side effects were increased appetite, common cold symptoms, headaches, and sedation.

Discussion

This was a prospective, open-label treatment trial of risperidone or olanzapine for the treatment of acute mania in preschool-age children with bipolar I and bipolar disorder NOS. Intent-to-treat analysis showed that subjects demonstrated statistically significant improvement in manic symptoms with both

risperidone and olanzapine. In addition, treatment with risperidone was also associated with a statistically significant improvement in symptoms of depression. A greater increase in prolactin level was observed in children treated with risperidone and a greater amount of weight gain was observed in those treated with olanzapine. To our knowledge, this study represents the first systematic evaluation of atypical antipsychotics in preschool children with bipolar disorder.

A statistically significant improvement in manic symptoms was observed within 1 week of treatment with risperidone and 2 weeks of treatment with olanzapine, indicating that these treatments rapidly exert their beneficial effects. This may be an important clinical advantage considering that the severity of pediatric bipolar disorder requires urgency in attaining rapid clinical control of severe aberrant symptoms.

The rate of response observed in the preschool-age children in our study is consistent with results documented in large randomized clinical trials of adults with bipolar disorder treated with olanzapine (Tohen et al 1999) and risperidone (Yatham 2003). Our results in preschoolers were also consistent with those previously observed using the same com-

Table 3. Metabolic Variables at Baseline and End Point (Mean \pm SD) in Risperidone or Olanzapine Open Study over 8 Weeks

	Risperidone		Olanzapine		Between Group p Value
	Baseline	End Point	Baseline	End Point	
Cholesterol (mg/dL)	161.3 \pm 40.1	157.8 \pm 32.7	150.8 \pm 32.7	159.6 \pm 27.2	F(1,27) = 1.0, p = .4
High density lipoprotein (mg/dL)	45.7 \pm 11.9	51.6 \pm 7.3	46.8 \pm 10.4	44.3 \pm 6.9	F(1,27) = 2.5, p = .1
Low density lipoprotein (mg/dL)	89.9 \pm 33.1	87.1 \pm 29.8	83.5 \pm 24.5	90.1 \pm 20.1	F(1,27) = .6, p = .5
Triglycerides (mg/dL)	128.4 \pm 109.9	95.3 \pm 50.8	101.6 \pm 47.3	126.5 \pm 59.5	F(1,27) = 2.4, p = .1
Glucose (mg/dL)	95.9 \pm 17.9	103.4 \pm 12.1	93.0 \pm 12.4	95.8 \pm 16.7	F(1,27) = .2, p = .6
Prolactin (ng/dL)	12.0 \pm 10.4	47.7 \pm 21.9 ^a	7.6 \pm 4.1	19.5 \pm 9.7 ^a	F(1,27) = 8.1, p = .009
Systolic Blood Pressure (mmHg)	98.2 \pm 9.6	108.0 \pm 11.5 ^a	104.1 \pm 14.4	109.6 \pm 12.7	F(1,30) = .7, p = .4
Diastolic Blood Pressure (mmHg)	60.4 \pm 8.3	60.3 \pm 8.5	64.8 \pm 17.3	63.5 \pm 6.3	F(1,30) = .1, p = .8
Pulse (bpm)	99.1 \pm 13.6	106.3 \pm 14.7	91.8 \pm 12.6	108.8 \pm 11.7	F(1,30) = 2.3, p = .1
Weight (kg)	22.4 \pm 3.5	24.6 \pm 4.1 ^a	20.8 \pm 4.8	24.0 \pm 5.3 ^a	F(1,27) = 2.0, p = .2

^ap < .05 versus baseline within risperidone or olanzapine arms.

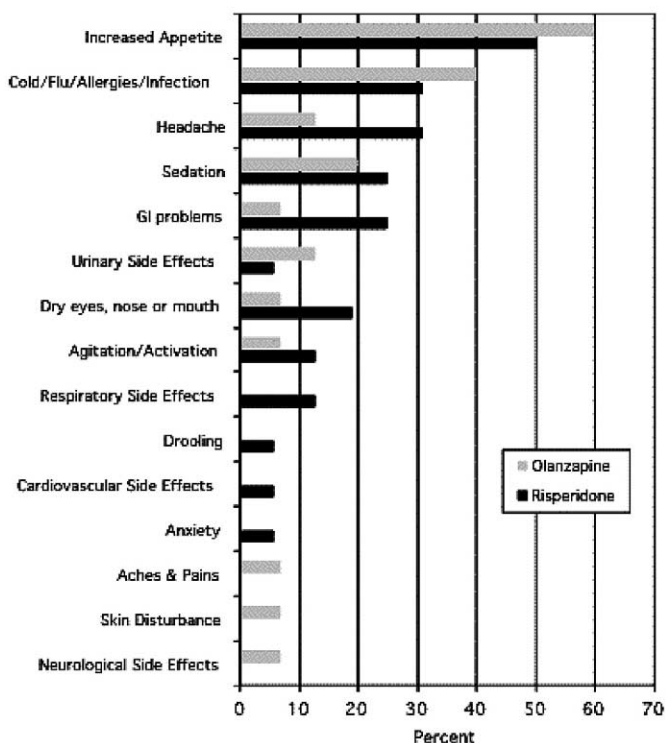


Figure 3. Side effects and adverse events.

pounds in older children with an identical study design. Previously reported open-label trials in children aged 6 to 17 years documented response rates of 61% after 8 weeks of olanzapine monotherapy (Frazier et al 2001) and 70% after 8 weeks of risperidone monotherapy (Biederman 2005).

Treatment with risperidone, but not olanzapine, was associated with a statistically significant improvement of depressive symptoms. This is consistent with our previous open-label study of risperidone in older children (Biederman 2005). Considering that the majority of children with bipolar disorder have mixed presentations (Wozniak et al 1995), the management of these constellation of symptoms is of high clinical relevance.

In contrast, we did not find a robust response to symptoms of disruptive behavioral disorders (DBD) as has been documented for atypical antipsychotics in the literature (e.g., Aman et al 2002). It is not clear why the clinical response observed in these subjects was less than the effect size documented in other samples, but it may be due to differences in the composition of the sample because other studies have not included preschool children with bipolar disorder. More work is needed to further evaluate this important issue.

Treatment with both risperidone and olanzapine were generally well tolerated, with only one subject dropping out because of adverse events (one olanzapine-treated subject dropped from the study because of increased appetite and hand tremor). There were no differences between study groups in the rate of spontaneously reported adverse events. Most commonly reported adverse effects included increased appetite, headache, and sedation. Many subjects (> 30%) also reported colds and flulike symptoms, but these were not considered related to the study treatment. Risperidone was associated with an increase in prolactin levels, but olanzapine

was not. In addition, there was statistically significant increase in weight from baseline to end point in subjects treated with both risperidone ($2.2 \pm .4$ kg) and olanzapine ($3.2 \pm .7$ kg). Because our trial was of a short duration, we can make no conclusions regarding the safety of long-term use of these agents in this population. Moreover, considering the young age of these children and that bipolar disorder may be chronic disorder in this population, the increased weight gain and prolactin elevation may be of particular concern in light of growing concerns that these adverse effects could lead to health complications (e.g., diabetes, gynecomastia, etc.). Thus, a careful risk–benefit assessment of the risks associated with these treatments and the risk associated with not treating mania in very young children should be undertaken when treating this population.

These results must be considered in light of methodologic limitations. Clearly, the results of this study need to be considered preliminary because of its uncontrolled nature. This was an open study; therefore, the assessments were not blind to treatment. Thus, firmer conclusions regarding the role of risperidone and olanzapine in the treatment of pediatric bipolar disorder await results from randomized, double-blind, controlled clinical trials. We also employed spontaneous reports of adverse effects that may have provided an underestimate of adverse events in these children; however, the high rate of relatively mild adverse effects reported in this study (such as cold symptoms) indicate that parents would have reported more serious adverse effects if they were evident.

Although we chose to use assessments accepted for use in older children to conduct this preliminary pilot study to begin the process of understanding treatment in this population, the rating scales and methods of assessment used in this study have not been validated in very young children. Thus, replication of these finding is needed when validated scales and instruments for the assessment of mania in preschoolers are further developed.

Despite these consideration, results from this prospective open study suggest that treatments with risperidone and olanzapine can result in a rapid reduction of symptoms of mania in preschool children with bipolar disorder. Nevertheless, because of the substantial residual symptomatology and adverse effects observed, there is a pressing need for identifying additional safe and effective treatments for the management of bipolar disorder in this high-risk population.

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