

A One-Year Open-Label Trial of Risperidone Augmentation in Lithium Nonresponder Youth with Preschool-Onset Bipolar Disorder

Mani N. Pavuluri, M.D.,¹ David B. Henry, Ph.D.,¹ Julie A. Carbray, D.N.Sc.,¹ Gwen A. Sampson, M.A.,¹ Michael W. Naylor, M.D.,¹ and Philip G. Janicak, M.D.²

ABSTRACT

Objective: The aim of this study was to assess the safety and efficacy of risperidone augmentation of lithium in preschool-onset bipolar disorder (BD) among youth who insufficiently respond to lithium monotherapy.

Method: Thirty-eight subjects between the ages of 4 and 17 years (mean age = 11.37 ± 3.8 years) with onset of BD in preschool years (manic or mixed episode) entered this 12-month trial. All subjects received lithium monotherapy. Patients who failed to adequately respond to lithium monotherapy after 8 weeks and those who relapsed after an initial response were given risperidone augmentation for up to 11 months. The Young Mania Rating Scale (YMRS) was the primary outcome measure. Response was defined as a $\geq 50\%$ decrease from baseline. Additional data were collected on diagnostic comorbidity, family history, number of hospitalizations, perinatal risk factors, history of physical or sexual abuse, Child Depression Rating Scale—Revised (CDRS-R), Clinical Global Impression (CGI) scale for BD (CGI-BP), Children's Global Assessment Scale (C-GAS), and adverse medication effects.

Results: Of the 38 subjects treated with lithium monotherapy, 17 responded, whereas 21 required augmentation with risperidone. Response rate in the youths treated with lithium + risperidone was 85.7% ($n = 18/21$). Significant predictors of inadequate response to lithium monotherapy requiring augmentation were: (1) attention-deficit/hyperactivity disorder (ADHD), (2) severity at baseline, (3) history of sexual or physical abuse, and (4) preschool age. Combination treatment of lithium and risperidone was found to be safe and well tolerated.

Conclusions: A substantial proportion of youth with a history of preschool-onset BD treated with lithium were either nonresponders or partial responders. Subsequent augmentation of lithium with risperidone in these cases was well tolerated and efficacious. Potential predictors of lithium nonresponse identified in this study may guide the choice of medications earlier in the treatment process.

¹Pediatric Bipolar Research Program, Department of Psychiatry, University of Illinois at Chicago (UIC), Chicago, Illinois.

²Rush-Presbyterian St. Luke's Medical Center, Chicago, Illinois.

MNP received research support from Marshall Reynolds Foundation, NIH MO1-RR-13987, Campus Research Board Award, Janssen Research Foundation, which supported this study.

INTRODUCTION

RECENTLY PUBLISHED PRACTICE guidelines for pediatric-onset bipolar disorder (BD) recommend the use of mood-stabilizer monotherapy, with an option of augmentation with a second mood stabilizer or second-generation antipsychotic (SGA) for nonresponders (Kowatch et al. 2005). Common practice when treating any disorder, including BD, is to begin with first-line treatments and augment when necessary (Emslie et al. 2004; Kowatch et al. 2003; Pavuluri et al. 2004a; Pliszka et al. 2003). Lithium is one of the preferred first-line treatments of mania in adults and was consistently demonstrated to be superior to placebo in alleviating manic symptoms (Bowden et al. 2005; Small et al. 1991; Segal et al. 1998; Bowden et al. 1994). Furthermore, lithium reduced the relapse rate in adult bipolar disorder and thus is an attractive treatment choice for long-term studies. Despite the paucity of data in pediatric BD, lithium is still the most studied mood stabilizer (McKnew et al. 1981; Delong and Nieman. 1983; Gram and Rafaelson 1972; Lena 1979; Kowatch et al. 2000), with the majority being short-term trials. There were three well-conducted randomized, monotherapy trials that involved a lithium arm (Geller et al. 1998a; Findling et al. 2005; Kowatch et al. 2000). The first was an open-label, randomized trial of lithium, divalproex sodium, and carbamazepine for bipolar disorder I and II in youth 8 and 18 years of age (Kowatch et al. 2000). Response rates in this study were 53% with divalproex sodium, 38% with lithium, and 38% with carbamazepine, with no significant difference between the groups. The second study was a double-blind, placebo-controlled, 6-week trial in youth with bipolar I or II and major depression with bipolar risk factors. All subjects had comorbid substance abuse (Geller et al. 1998a). Lithium was more efficacious than placebo in improving global functioning while reducing the percent of subjects with positive urine drug screens. The third study was a maintenance trial, using a double-blind design comparing lithium to divalproex sodium over 18 months in stable, euthymic bipolar I and II subjects. Children and adolescents between the ages of 5 and 17 years

were enrolled (Findling et al. 2005). Although lithium was as effective as divalproex in postponing relapse, at the end of 18 months, only 3 subjects remained in each arm. The majority of those on lithium monotherapy did not remain in the trial for more than 4 months. In summary, lithium monotherapy was effective over the short term in nearly half of those treated and prevented relapse but did not appear to be effective in maintaining recovery beyond 4 months.

Evidence is accumulating that augmentation of lithium is effective in acute (Findling et al. 2003a; Kowatch et al. 2003; Kafantaris et al. 2004; 2001a,b) and six-month, (Pavuluri et al. 2004b) prospective trials of pediatric BD. Kafantaris et al. (2001a,b; 2004) examined severely ill manic adolescents and reported that antipsychotics plus lithium were superior to lithium monotherapy, as subjects worsened after discontinuation of the antipsychotic. SGAs, in particular, appear to be efficacious in combination with mood stabilizers in treating acute symptoms of pediatric BD (DelBello et al. 2002; Kafantaris et al. 2002a,b; Pavuluri et al. 2004c).

Among the SGAs, risperidone has been extensively tested in pediatric populations and has been found to be safe (Armenteros et al. 1997; McCracken et al. 2002; Snyder et al. 2002; a et al. 2002; Buitelaar et al. 2001; Findling et al. 2000; Gaffney et al. 2002). Risperidone was also efficacious and safe in pediatric BD, alone (Biederman et al. in press) or in combination (Pavuluri et al. 2004b). Considering the evidence for its efficacy and safety alone or in combination with lithium for up to 6 months, risperidone appears to be a viable augmentation choice with first-line mood stabilizers.

Factors predicting the need for augmentation with a second agent will help tailor the treatment. Clinical variables, including comorbid attention-deficit/hyperactivity disorder (ADHD), younger age, abuse and severity of illness, may be potential predictors of poor lithium response. For example, the presence of comorbid ADHD was associated with poor response to lithium in some studies (Strober et al. 1988, 1998) but not in another (Kafantaris et al. 2003). Also, a history of sexual and/or physical abuse was associated with earlier onset of

bipolar illness and poorer response to treatment (Leverich et al. 2002). Detecting such factors may avoid therapeutic delay by introducing a more appropriate pharmacological strategy, such as combination pharmacotherapy.

Research suggests that preschool age of onset may predict for a more virulent course (Wilens et al. 2002) and require more intense intervention. Children with very early onset may go untreated or be offered inappropriate treatments that complicate the clinical course. The number of case reports identifying preschool-onset BD is steadily increasing (Cesena et al. 2002; Mota-Castillo et al. 2001; Pavuluri et al. 2002a; Poznanski et al. 1984b; Tuzun et al. 2002). Phenomenological studies are yielding detailed descriptions of pediatric BD (Geller et al. 2002a), and attempts are now being made to carefully characterize these children (Task Force on Research Diagnostic Criteria: Infancy and Preschool 2003), with the aim of providing more appropriate treatment.

Thus, we studied children and adolescents with a history of preschool-onset BD: (1) To determine the safety and efficacy of risperidone augmentation for manic and mixed episodes in those who did not respond to lithium monotherapy and (2) to determine the predictors of nonresponse to lithium monotherapy. Based on the nonresponse rates found in previous studies (Kowatch et al. 2000) and the greater severity of preschool-onset BD, we hypothesized that substantially more than half of subjects with preschool onset would respond insufficiently to lithium monotherapy. We further hypothesized that the augmentation with risperidone would prove to be safe and effective. Based on the literature, we hypothesized that comorbid ADHD, earlier age of onset, and severe stressors, such as child abuse, would be predictors of poor response to lithium.

METHOD

This was a 12-month, single-site, prospective, open-label, outpatient study of preschool-onset BD. The study was approved by the University of Illinois at Chicago (UIC; Chicago IL) Institutional Review Board. Parents signed

consent, and children gave assent to participate in this trial.

Subjects

Patients that were consecutively referred to our Pediatric Mood Disorders Program were screened. Inclusion criteria were: (1) Age between 4 and 17 years; (2) a *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) diagnosis (American Psychiatric Association 1994) of current BD, manic or mixed episode with onset of illness prior to their 5th birthday; (3) baseline Young Mania Rating Scale (YMRS; Young et al. 1978) score ≥ 20 ; and (4) involvement of a parent or guardian who could provide longitudinal history. Exclusion criteria included: (1) Evidence of active substance abuse; (2) mental retardation; (3) active suicidal ideation or behavior; (4) the presence of neurological or medical problems; (5) a history of intolerance to lithium levels of ≥ 0.6 mmol/L; or (6) children and adolescents under the guardianship of the Department of Child and Family Services or those experiencing current physical or sexual abuse.

Assessment procedures

Each child and the parent or legal guardian were interviewed using the Washington University at St. Louis Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS; Geller et al. 1998b). The WASH-U-KSADS interviews were completed by a trained masters-level research assistant (GS), a doctoral-level nurse practitioner in child psychiatry (JC), or by a board-certified child and adolescent psychiatrist (MP). Live diagnostic interviews of 10 cases were rated by these three researchers to establish interrater reliability. By Cohen's Kappa, reliability of diagnosis was 0.96 between MP and GS and 0.98 between MP and JC. Overall reliability of symptom identification was 0.93–0.96 among the three interviewers. In addition, all patients underwent a standard clinical assessment consisting of a diagnostic interview with the patient and family. Data from all sources were combined to make a consensus clinical diagnosis to decrease the

likelihood of false positives in very young children. Diagnostic differences were resolved in a weekly consensus conference involving the research team (MP, JC, and GS). Family psychiatric history was obtained using the Family History Screen (FHS; Weissman et al. 2000), revised with the author's permission to include the grandparents' histories. In addition, interviewers collected data on hospitalizations, perinatal risk factors, temperament, and a history of physical or sexual abuse. These variables (along with information on psychopathology) equate with a standard clinical history and were previously reported to be specifically relevant in pediatric BD (Chang et al. 2003; Geller et al. 1998b, 2002b; Hyun et al. 2000; Leverich et al. 2002; Pavuluri et al. 2002b).

Physical examination and laboratory assessments were also obtained. Lab values included lithium levels, prolactin levels, thyroid function tests (TFTs), liver function tests, calcium, phosphorous, uric acid, glucose, total protein, albumin, cholesterol, creatinine kinase, electrolytes, urinalysis with urine drug screen, a pregnancy test for females of child-bearing age, a complete blood cell count, and a baseline electrocardiogram (ECG). Height, weight, blood pressure, and heart rate were also obtained. In medication-naïve subjects, the physical examination and laboratory studies were not repeated if they had been conducted within the past 3 months. Extrapyrimal symptoms (EPS) were assessed using the Abnormal Involuntary Movement Scale (AIMS; Guy 1976). Adverse events were recorded using a comprehensive checklist developed by our research team (i.e., Pediatric Side Effects Checklist, P-SEC; Pavuluri and Janicak 2004).

Efficacy and safety measures

The primary efficacy measure was the YMRS (Young et al. 1978). Secondary measures included the Child Depression Rating Scale—Revised (CDRS-R; Poznanski et al. 1984a), Clinical Global Impression (CGI) scale for BD (CGI-BP; Spearing et al. 1997), and Clinical Global Assessment Scale (C-GAS; Shaffer et al. 1983). Two board-certified child and adolescent psychiatrists and a doctoral-level nurse (MP, MN, and JC) had previously established

interrater reliability for each rating scale (Pavuluri et al. 2005). MP and JC completed all ratings by interviewing the subject and his or her primary caregiver. Subjects were monitored every 1–2 weeks during the first month of the trial as a part of standard care for acutely ill subjects who had recently been taken off or were on no medications. Ratings were obtained on a monthly basis.

To monitor safety, laboratory assessments were obtained on a monthly basis, except for prolactin, TFT, and ECG, which were repeated every 3 months. The P-SEC and AIMS were completed each month by a research nurse in collaboration with the subjects and their primary caregivers.

Augmentation based on response

Clinical response was defined as a $\geq 50\%$ change from the baseline YMRS score. Clinical remission was defined as a change from the baseline YMRS score $\geq 50\%$; ≤ 12 final score; and a CGI-BP—Improvement score ≤ 2 (1 = much improved and 2 = very much improved); and a final CGAS ≥ 51 . All other subjects were defined as nonresponders at endpoint. Risperidone augmentation was initiated if there was a $\leq 50\%$ change from the baseline YMRS score at any point after 8 weeks of lithium monotherapy with a minimum of 6 weeks at a therapeutic level. All subjects were assessed on a monthly basis (baseline and 12 follow-up visits). Response and need for augmentation were determined from 2 to 11 months after the initial trial of lithium monotherapy. Subjects were not eligible for augmentation after the 11th month.

Pharmacotherapy

Lithium was the initial mood stabilizer for all subjects. Treatment was initiated with a single dose of 150 or 300 mg (10–30 mg/kg/day) and increased by 150 or 300 mg every 3 days to achieve a therapeutic plasma level (i.e., 0.6–1.0 meq/liter at trough) that is conducive to “adequate” clinical progress (Kowatch et al. 2000). The lithium dose was held constant following the introduction of risperidone augmentation. Risperidone was initiated at 0.25 mg per day

and titrated by increments of up to 0.25–0.5 mg every 2 days to achieve the maximum tolerable level by day 7. The maximum allowable dose was 2 mg per day. This lower dose was chosen, as risperidone was used as an augmentor and not the primary treatment, and data suggest that this dose is adequate for most outpatients (Pavuluri et al. 2004a). We employed a flexible dosing strategy instead of a forced titration to the maximum allowable dose, balancing efficacy with safety and tolerability.

Subjects with a history of ADHD when not actively manic or depressed, who benefited from psychostimulants at U.S. Food and Drug Administration (FDA)-approved doses and were not negatively affected by them at study entry, were continued on these medications. Further dose or brand changes were not permitted during the trial period. If subjects were not benefiting from psychostimulants at study entry by parent report, these drugs were discontinued. Clonidine (up to 0.3 µg/kg per day) was allowed as a rescue medication to treat agitation (Bassarath 2003) to a maximum of 3 doses per week for a total of 3 weeks over 12 months. Otherwise, no other medications were allowed. Subjects were off all medications (no subjects were on fluoxetine just prior to the study entry that would have required a 5-week tapering period) for a wash out period of 4–7 days before starting lithium.

Data analysis

We divided the sample according to subjects' needs for augmentation (i.e., those who remained on lithium monotherapy for the full 12 months versus those who received augmentation therapy, as described above).

We evaluated demographic differences between the two groups, as well as three sets of variables possibly associated with insufficient response to lithium: (1) Symptom type and severity; (2) family history variables; and (3) patient history variables. Because the sample size was insufficient to employ in a logistic regression model, we used *t* tests for continuous variables and chi-square tests for categorical variables. To reduce the possibility of experiment-wise error inflation, we only interpreted differences at the conservative alpha level of 0.01.

We used intent-to-treat (ITT) analyses (Fisher et al. 1990) with last observation carried forward (LOCF) to assess treatment response in the two groups. To determine the overall effect of augmentation on symptoms, we compared mean initial and final scores on the YMRS, CDRS-R, CGI, and C-GAS using multivariate analysis of variance (MANOVA) with time (pre-, post-treatment) and assessment measures as within-subjects factors and augmentation as a between-subjects factor. Finally, to examine the patterns of response, we plotted scores on the YMRS and CDRS-R over the course of treatment for both groups.

RESULTS

Subjects

A total of 64 subjects underwent the diagnostic interview at our Pediatric Mood Disorders Program. Forty-five subjects fulfilled the inclusion criteria. Thirty-eight subjects completed ratings on at least two occasions and were included in the analyses. The seven subjects excluded from the study included 2 who were inadequately dosed because of side effects with lithium and dropped out before the completion of assessment on the first visit; 2 who moved out of the area before completing 1 month of treatment; 1 who declined to accept study medication; and 2 who could not be located for follow-up after initial enrollment. The Consolidated Standards of Reporting Trials (CONSORT) flow chart of this trial is depicted in Figure 1. The length of time subjects received study medication ranged from 6 to 52 weeks (mean = of 31.4 [± 18] weeks).

Demographics and clinical pattern

Demographic information for the overall sample, the group that required risperidone augmentation (lithium+risperidone), and the group that did not require augmentation (lithium monotherapy) is summarized in Table 1. There were no significant differences between these two groups on any of the demographic variables considered.

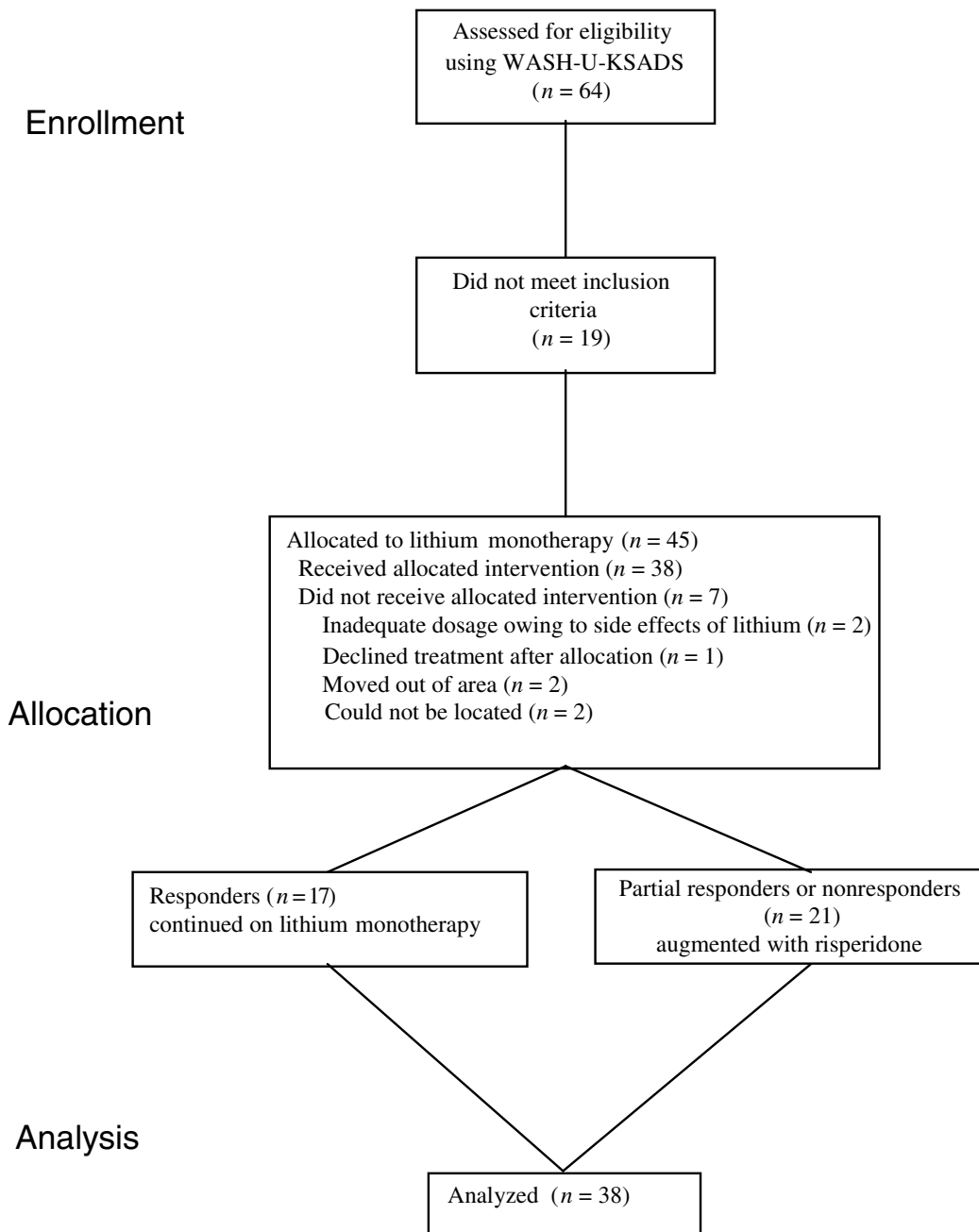


FIG. 1. CONSORT flow chart of risperidone augmentation of lithium in preschool-onset bipolar disorder study. CONSORT = The Consolidated Standards of Reporting Trials.

Variables associated with poor response to lithium

To examine the variables that characterized partial response or nonresponse to lithium, we conducted *t* tests and chi-square tests comparing responders and insufficient responders on initial severity, family history, and patient history variables. The results are reported in Table 2.

The first panel of Table 2 shows the results from the analysis of initial symptom severity. Initial severity of ADHD symptoms was significantly associated with a higher probability of insufficient response to lithium monotherapy ($p < 0.001$). The second panel of Table 2 shows the results from the analysis of family history variables, none of which were significantly associated with insufficient response to

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF STUDY SAMPLE, BY TREATMENT GROUP (N = 38)

Variables	Mean (\pm SD) or percent of sample		
	Lithium (n = 17)	Lithium + risperidone (n = 21)	Total sample (N = 38)
Demographic Characteristics			
Mean age in years (SD)	12.5 (\pm 3.12)	10.48 (\pm 4.13)	11.37 (\pm 3.80)
Mean socioeconomic status (SD)	2.35 (\pm 1.73)	2.95 (\pm 1.43)	2.68 (\pm 1.58)
Ethnicity (%)			
African-American	31.3%	14.3%	21.6%
Caucasian	56.3%	66.7%	62.2%
Hispanic	12.5%	19.0%	16.2%
Gender (males)	70.6%	81.0%	76.3%
Comorbid Diagnosis (%)			
ADHD	64.7%	90.5%*	78.9%
Oppositional defiant disorder	41.2%	52.4%	47.4%

ADHD = attention-deficit/hyperactivity disorder.

SD = standard deviation; * $p < 0.01$.

lithium monotherapy. The third panel of Table 2 reports the analysis of patient history variables. Preschool age at the first visit and history of physical or sexual abuse were significantly associated with poor response to lithium monotherapy ($p < 0.01$). Of the 13 subjects (34.2%) who had a history of abuse, only 1 had posttraumatic stress disorder (PTSD) and responded to lithium monotherapy.

Symptomatic response in ITT sample

Of the 38 subjects initially treated with lithium, 17 (44.7%) responded to lithium monotherapy over the entire 12 months of the study. Figure 2 shows the pattern of response on the YMRS and CDRS-R for those in the lithium monotherapy group.

Twenty-one subjects (55.3%) were insufficient responders after a minimum of 8 weeks and were augmented with risperidone. At the end of 12 months, the response rate, as defined by a >50% reduction from baseline on the YMRS, was 85.7% ($n = 18/21$) in the augmented group. The modal time at which augmentation began was 8 weeks, and the median was 13 weeks. Figure 3A shows the length of treatment in months from the date of augmentation. No subject participated in the study for more than 12 months. However, the lengths of

time prior to and following augmentation differed substantially among the children. Figure 3B shows the response pattern for initial poor responders to lithium monotherapy, who then received risperidone augmentation. As with Figure 3A, these averages are centered at the point of augmentation. Of the 17 subjects who were lithium responders, 9 (53%) achieved remission (YMRS score $\geq 50\%$ change from baseline and ≤ 12 final score + CGI-BP-I ≤ 2 + CGAS ≥ 51). Among the augmented group, 57.1% (12/21) maintained remission at the end of 12 months. Treatment response is summarized in Table 3.

Medication dosing

At the end of the study (EOS), the mean (standard deviation) total daily dose for the lithium responders was 825 (\pm 350) mg/day, with an average EOS blood level of 0.92 mmol/L. The mean dose (standard deviation) of lithium among those augmented with risperidone was 775 (\pm 400) mg/day, with an average EOS level of 0.87 mmol/L. In the augmented group, the mean dose of risperidone was 0.99 (\pm 0.48) mg.

Concomitantly administered medications included stimulants in 30% (monotherapy: $n = 2$; augmentation: $n = 9$) and clonidine in 23.7% (monotherapy: $n = 1$; augmentation: $n = 8$).

TABLE 2. VARIABLES ASSOCIATED WITH INSUFFICIENT LITHIUM RESPONSE ($N = 38$)

Variable	Means or percentages		t(36) or χ^2 (1, $N = 38$) ^a
	Lithium (n = 17)	Lithium + risperidone (n = 21)	
Initial Symptom Severity Variables			
Mean CGI ADHD severity at first visit	3.88	5.52	3.69**
Mean CGI psychosis severity at first visit	2.12	3.05	1.57
Mean CGI aggression severity at first visit	5.18	5.67	1.29
Mean CGI depression severity at first visit	3.94	4.24	0.57
Mean CGI mania severity at first visit	5.35	5.95	2.21
Mean CGI sleep problems severity at first visit	3.12	3.90	1.31
Mean CGI overall severity at first visit	5.53	6.00	1.83
Suicidal ideation and behavior at first visit	58.82%	38.10%	1.62
Thought disorders at first visit	94.10%	100.00%	1.27
Grandiosity at first visit	82.40%	90.50%	0.54
Family History Variables			
Bipolar disorder	53.3%	66.7%	0.65
Depression	62.5%	57.1%	0.11
Alcoholism	43.7%	28.6%	0.92
Drug abuse	43.7%	33.3%	0.41
Patient History Variables			
Special education	64.7%	76.2%	0.60
Previous hospitalization	29.3%	14.3%	1.94
Perinatal risk	18.8%	28.6%	0.48
Difficult temperament	50.0%	66.7%	1.05
Preschool age at first visit	0.0%	33.3%	6.94*
History of antidepressant use	35.3%	47.6%	0.58
History of stimulant use	52.9%	66.7%	0.74
History of physical or sexual abuse	19.0%	52.9%	4.79*

Note. $N = 38$.

CGI = Clinical Global Improvement; ADHD = attention-deficit/hyperactivity disorder.

^at tests are used to compare means, χ^2 tests to compare proportions.

* $p < 0.01$; ** $p < 0.001$.

EOS medications were limited to stimulants in 30% ($n = 11$). With regard to comorbid ADHD ($n = 30$; 78.9%), among augmented subjects with comorbid ADHD, a significantly higher percent (53%) received stimulants during the study than did monotherapy subjects with comorbid ADHD (18%) (chi-square [1, $n = 38$] = 4.87; $p < -0.05$).

Medication tolerability

Two subjects withdrew from the study because of lithium intolerance. The most common adverse events reported by the subjects and/or their guardians, at least once during the treatment trial, are summarized in Table 4.

There were no significant differences between groups for any of these adverse events.

The mean (standard deviation) baseline weight of study participants was 40.6 (+ 4.2) kg, and at EOS, 44.1 (+ 4.4) kg. The weight gain from baseline to EOS was within expected limits, according to weight charts provided by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC 2003) for both genders and age groups. Laboratory parameters were normal in all subjects except for prolactin elevation in 2 subjects on risperidone (58 $\mu\text{g/L}$ and 49 $\mu\text{g/L}$). There were no reported clinical sequelae associated with the prolactin elevation in these 2 subjects, and neither subject was discontinued from the study.

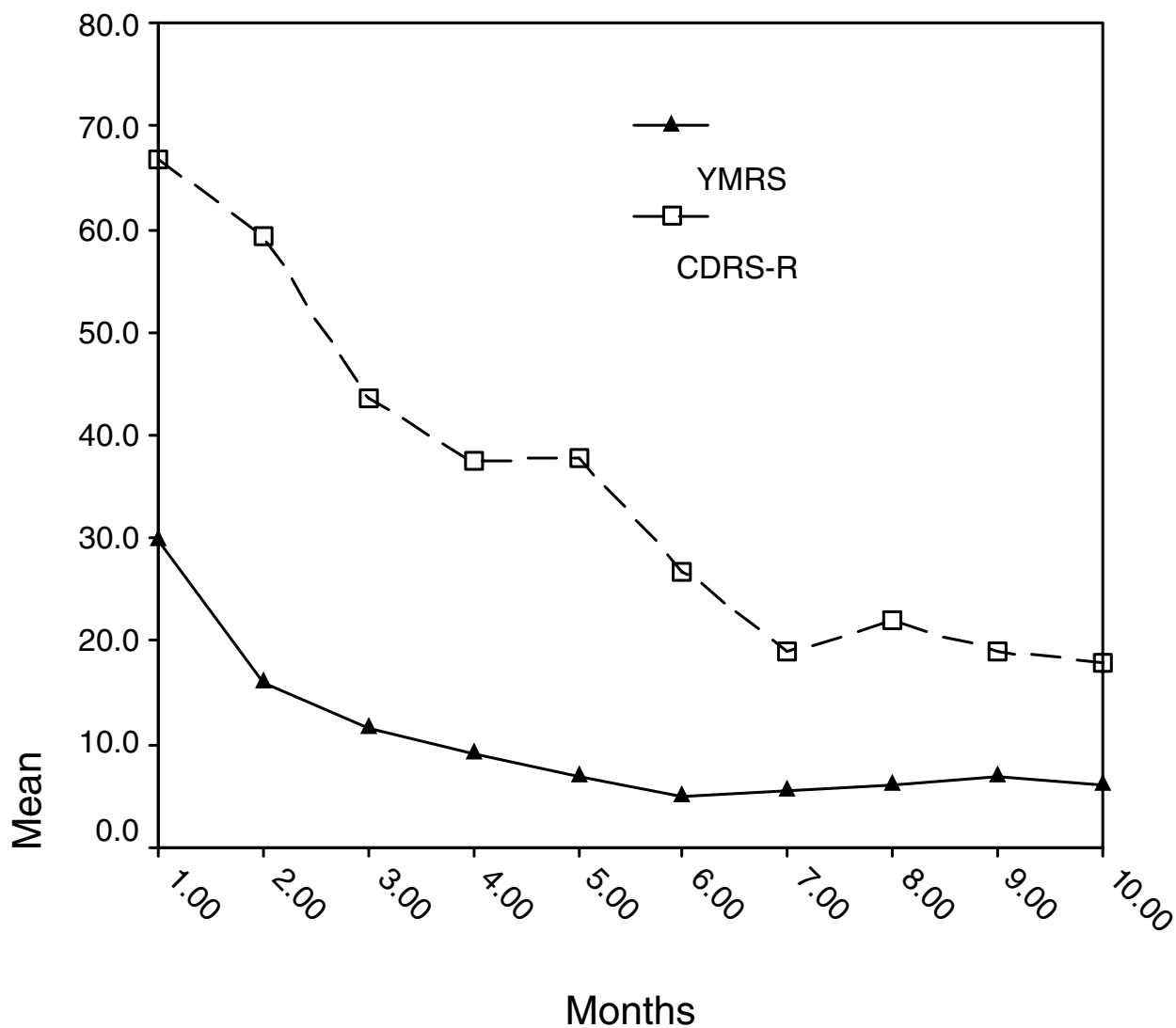
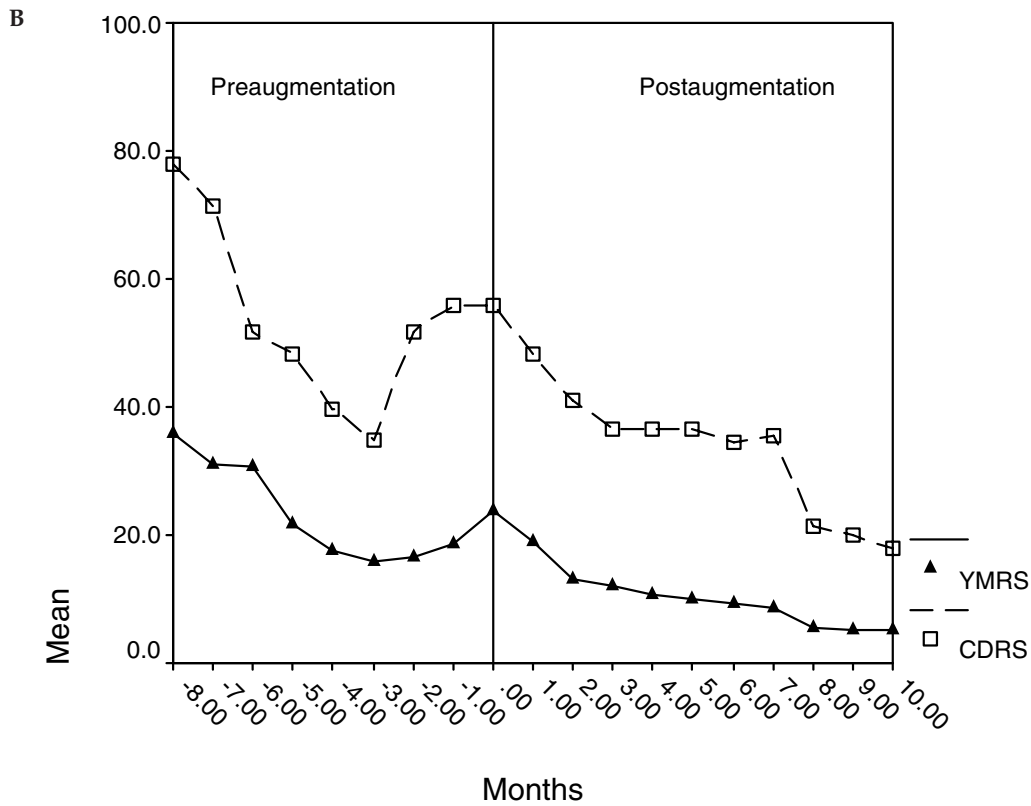
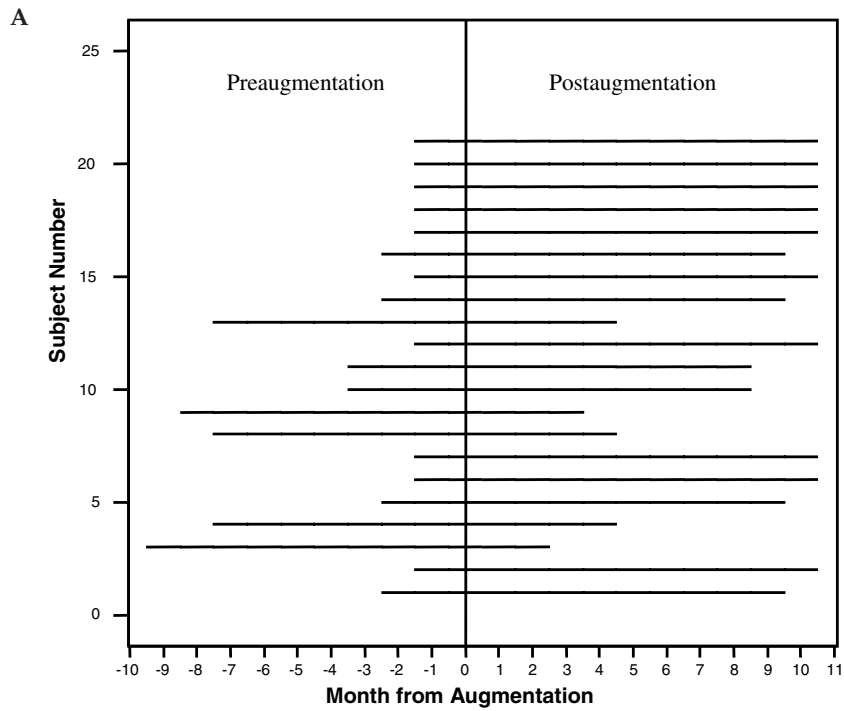


FIG. 2. Child Depression Rating Scale—Revised (CDRS-R) and Young Mania Rating Scale (YMRS) scores over the course of treatment: Lithium monotherapy group ($n = 17$).

TABLE 3. END-OF-STUDY (EOS) TREATMENT RESPONSE

Variable	Lithium ($n = 17$)	Lithium + risperidone ($n = 21$)	Total sample ($N = 38$)
Treatment response			
YMRS mean (SD)	7.06 (\pm 4.28)	7.43 (\pm 4.51)	7.26 (\pm 4.35)
CGI-S mean (SD)	1.64 (\pm 0.80)	1.89 (\pm 0.76)	1.78 (\pm 0.78)
CDRS-R mean (SD)	30.94 (\pm 9.75)	29.47 (\pm 9.91)	30.14 (\pm 9.72)
CGI-I overall ≤ 2 (%)	76.5%	66.7%	71.1%
C-GAS	57.65 (\pm 7.89)	55.14 (\pm 6.03)	56.26 (\pm 6.94)

YMRS = Young Mania Rating Scale; CGI-S = Clinical Global Impression—Severity; CDRS-R = Child Depression Rating Scale—Revised; CGI-I = Clinical Global Impression—Improvement; C-GAS = Children's Global Assessment Scale; SD = standard deviation.



CDRS-R and YMRS scores over the course of treatment. Lithium + risperidone group, $n = 21$. Vertical centerline indicates point of augmentation. Negative numbers are months prior to augmentation, and positive numbers are months following augmentation.

FIG. 3. (A) Duration of treatment in months by subject, centered at the point of augmentation. Lithium + risperidone group ($n = 21$). Vertical line indicates point of augmentation, and negative numbers are months prior to augmentation. Positive numbers are months following augmentation. (B) Child Depression Rating Scale—Revised (CDRS-R) and Young Mania Rating Scale, (YMRS) scores scores over the course of treatment: Lithium + risperidone group, ($n = 21$). Vertical line indicates point of augmentation. Negative numbers are months prior to augmentation and positive numbers are months following augmentation.

TABLE 4. MOST COMMON ADVERSE EVENTS REPORTED IN CHILDREN WITH PRESCHOOL-ONSET BD

Adverse event	Percent (n)	
	Lithium (n = 17)	Lithium + risperidone (n = 21)
Weight gain	41.2 (7)	52.4 (11)
Nausea/vomiting	41.2 (7)	42.9 (9)
Increased appetite	35.3 (6)	47.6 (10)
Stomach pain	41.2 (7)	38.1 (8)
Sedation	35.3 (6)	33.3 (7)
Polyuria	17.6 (3)	23.8 (5)
Enuresis	23.5 (4)	23.8 (5)
Tremor	41.2 (7)	38.1 (8)
Restlessness	29.4 (5)	33.3 (7)
Stiffness of muscles	5.9 (1)	14.3 (3)
Fatigue	29.4 (5)	21 (6)
Cognitive dulling	35.3 (6)	33.3 (7)
Flu-like symptoms	17.6 (3)	19 (4)

BD = bipolar disorder.

DISCUSSION

Our central finding was that in those insufficiently responding to lithium monotherapy, risperidone augmentation produced an 85.7% response rate. Augmentation with risperidone was well tolerated, with no serious adverse events. Among children with preschool-onset BD, the response rate on monotherapy was less than half and was similar to that demonstrated by Kowatch et al. (2000). Similarly, the response rate on the combination regimen was similar to the rates reported in studies using a mood stabilizer plus a second generation antipsychotic (DelBello et al. 2002; Kafantaris et al. 2001a,b; Kowatch et al. 2003; Pavuluri et al. 2004b).

There were two additional observations in relation to the trajectory of response over 12 months. The majority of subjects improved in a manner consistent with the pattern shown in Figure 2 (i.e., rapid improvement for the first few months, followed by more gradual improvement). A few subjects on lithium monotherapy showed gradual improvement over the 12 months of the study. Secondly, among those that were subsequently augmented, there was a transient initial reduction in depressive symptoms, and to a lesser degree, in manic symptoms, with lithium mono-

therapy. As is shown in Figure 3B, sustained improvement and persistent decline in symptoms were noted only after augmentation in this group.

Variables associated with insufficient response to lithium included ADHD severity at baseline, a history of physical or sexual abuse, and preschool age at time of study. Our results are similar to those of Strober et al. (1988, 1998), who found that comorbid ADHD was associated with poor response to lithium monotherapy. In our sample, a history of stimulant use did not predict augmentation, but a higher percentage of children in the augmented group were on stimulants during the study. It is conceivable that the use of stimulants may have impeded response to lithium monotherapy; however, the small sample size makes such a difference difficult to detect. The effects of stimulants in this population are unclear, with some studies reporting a worsening of mania with stimulants (Biederman et al. 1999, 2000; DelBello et al. 2001; Mota-Castillo et al. 2001; Soutullo et al. 2002) and others finding no negative effects (Carlson et al. 2002; Carlson 2003; Scheffer et al. 2005).

Our finding that a history of physical or sexual abuse was associated with poor response to lithium monotherapy is also consistent with previous reports. Leverich et al. (2002) found that such a history was associated with earlier onset of bipolar illness, greater comorbidity, accelerated cycling, a more severe course of illness, and treatment resistance. The causal direction is not clear. It is possible that abuse (physical, emotional, or sexual) may cause affect dysregulation, as has been shown in adult studies (Hyun et al. 2000; Leverich et al. 2002). Alternatively, it is possible that child abuse and treatment resistance are both caused by genetic predispositions to affective disorders (Hyun et al. 2000). It is also possible that the combination of genetic vulnerability and psychosocial stressors related to the abuse result in a more severe form of the illness, requiring augmentation and a greater need for rescue medications, such as clonidine.

We also found that preschoolers with BD were less likely than school-aged children to respond to lithium monotherapy and to require augmentation. Given the small sample

size of preschoolers in this study ($n = 8$), however, this observation must be interpreted with caution. This is the first study to suggest that preschool age at the time of illness onset may be associated with a poorer response to lithium among children with BD.

Prolactin elevation in 2 subjects on risperidone did not produce clinical symptoms during the trial period. The safety data in previously published risperidone trials suggest that there is an initial prolactin elevation at the end of 4–6 weeks, with subsequent reduction in levels on follow-up (Findling et al. 2003b). The clinical significance of this phenomenon needs to be explored in future studies.

In practice, clinicians either avoid medications in preschoolers until the disorder progresses or quickly proceed to combination strategies given the severity of symptoms with early-onset BD. This study provides empirical evidence advocating for the treatment of preschoolers and outlines the context for risperidone augmentation of lithium in both younger and older preschool-onset BD children. Although this study shows that lithium monotherapy may be sufficient for approximately 50% of children, it also suggests that many will benefit from augmentation. Overall, this measured approach for mood stabilization produced a good rate of clinical response in the sample. Our study also identified significant variables associated with inadequate response to lithium monotherapy that may indicate the need for augmentation. We attempted to bridge the gap of evidence-based research and community practice (McClellan and Werry 2003) by providing support for combination treatment in very young children.

Limitations

There were several limitations to our trial that need to be considered. Firstly, a history of preschool onset of illness was elicited from a lifetime diagnostic interview in the majority of the subjects and was not prospective in nature. To increase the accuracy, we utilized the WASH-U-KSADS, which has been shown to reliably elicit a lifelong history of the onset and offset of the BD symptoms (Geller et al. 1998b). Secondly, there is a lack of diagnostic instru-

ments for preschoolers. Because the WASH-U-KSADS was only validated for children over 8 years of age (Geller et al. 1998a), we also relied on our diagnostic acumen. Thirdly, this study was limited by the small sample of children with preschool onset and the small sample of preschool age children during the study. Results from larger multisite studies may yield more conclusive results. Fourthly, we did not randomize nonresponders to receive risperidone augmentation in this exploratory study. Thus, it is possible that continued use of monotherapy would have produced long-term results that may not differ from augmentation. Withholding a potentially effective treatment in a disabling disorder for 12 months is ethically problematic. Randomized, placebo-controlled trials, in which nonresponders are assigned either to augmentation or continued monotherapy, could provide more definitive evidence. Fifthly, the potential bias in diagnosis and outcome ratings inherent in any open trial may have been present in this study. To decrease the likelihood of bias, we used three trained diagnostic interviewers. Additionally, the outcome ratings were checked for reliability by a second board-certified child psychiatrist blinded to treatment condition.

CONCLUSIONS

In summary, we found that: More than half of these preschool-onset BD subjects did not respond to lithium; severity of ADHD at baseline, a history of physical or sexual abuse, and preschool-age illness onset were significantly associated with an increased likelihood of poor response to lithium monotherapy; and augmentation with risperidone in youth with preschool-onset BD with inadequate response to lithium monotherapy was safe and effective.

REFERENCES

- Aman MG, De Smedt G, Derivan A, Lyons B, Findling RL, Risperidone Disruptive Behavior Study Group: Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. *Am J Psychiatry* 159:1337–1346, 2002.

- American Psychiatric Association: Diagnostic And Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). Washington (DC), American Psychiatric Association, 1994.
- Armenteros JL, Whitaker AH, Welikson M, Stedje DJ, Gorman J: Risperidone in adolescents with schizophrenia: An open-pilot study. *J Am Acad Child Adolesc Psychiatry* 36:694–700, 1997.
- Bassarath L: Medication strategies in childhood aggression: A review. *Can J Psychiatry* 48:367–373, 2003.
- Biederman J, Mick E, Prince J, Bostic JO, Wilens TE, Spencer T: Systematic chart review of the pharmacological treatment of comorbid attention-deficit/hyperactivity disorder in youth with bipolar disorder. *J Child Adolesc Psychopharmacol* 156:1931–1937, 1999.
- Biederman J, Mick E, Spencer T, Wilens TE, Faraone SV: Therapeutic dilemmas in the pharmacotherapy of bipolar depression in the young. *J Child Adolesc Psychopharmacol* 10:185–192, 2000.
- Biederman J, Mick E, Wozniak J, et al.: An open-label trial of risperidone in children with bipolar disorder and comorbid attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* in press.
- Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, Dilsavv SC, Davis JM, Rush AJ, Small JG: Efficacy of divalproex versus lithium and placebo in the treatment of mania. The Depakote Mania Study Group. *JAMA* 271:918–924, 1994.
- Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, Vagrero M, Svensson K: A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* 66:111–121, 2005.
- Buitelaar JK, van der Gaag RJ, Cohen-Kettenis P, Melman CT: A randomized, controlled trial of risperidone in the treatment of aggression in hospitalized adolescents with subaverage cognitive abilities. *J Clin Psychiatry* 62:239–248, 2001.
- Carlson GA: The bottom line. *J Child Adolesc Psychopharmacol*, 13:115–118, 2003.
- Carlson GA, Bromet EJ, Driessens C, Mojtabai R, Schwartz JE: Age at onset, childhood psychopathology, and 2-year outcome in psychotic bipolar disorder. *Am J Psychiatry* 159:307–309, 2002.
- Centers for Disease Control and Prevention: Clinical Growth Charts from the National Health and Nutrition Examination Survey. Atlanta (Georgia), National Center for Health Statistics, 2003. Online document at: www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm.
- Cesena M, Gonzalez-Heydrich J, Szigethy E, Kohlenberg T, DeMaso D: A case series of eight aggressive young children treated with risperidone. *J Child Adolesc Psychopharmacol* 12:337–345, 2002.
- Chang KD, Blasey CM, Ketter TA, Steiner H: Temperament characteristics of child and adolescent bipolar offspring. *J Affect Disord* 77:11–19, 2003.
- DelBello M, Schwiers M, Rosenberg L, Strakowski S: A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 41:1216–1223, 2002.
- Delong GR, Nieman MA: Lithium-induced behavior changes in children with symptoms suggesting manic-depressive illness. *Psychopharmacol Bull* 19:258–265, 1983.
- DelBello MP, Soutullo CA, Hendricks W, Niemeier RT, McElroy SL, Strakowski SM: Prior stimulant treatment in adolescents with bipolar disorder: Association with age at onset. *Bipolar Disord* 3:53–57, 2001.
- Emslie GJ, Hughes CW, Crismon ML, Lopez M, Pliska S, Toprac MG, Boemer C, Texas Children's Medication Mental Algorithm Project (CMAP): A feasibility study of the childhood depression medication algorithm: The Texas Children's Medication Mental Algorithm Project (CMAP). *J Am Acad Child Adolesc Psychiatry* 43:519–527, 2004.
- Findling RL, Kusumakar V, Daneman D, Moshang T, De Smedt G, Binder C: Prolactin levels during long-term risperidone treatment in children and adolescents. *J Clin Psychiatry* 64:1362–1369, 2003b.
- Findling RL, McNamara N, Branicky L, Schluchter M, Lemon E, Blumer J: A double-blind pilot study of risperidone in the treatment of conduct disorder. *J Am Acad Child Adolesc Psychiatry* 39:509–516, 2000.
- Findling RL, McNamara NK, Gracious BL, Youngstrom EA, Stansbrey RJ, Reed MD: Combination lithium and divalproex sodium in pediatric bipolarity. *J Am Acad Child Adolesc Psychiatry* 42:895–901, 2003a.
- Findling RL, McNamara NK, Youngstrom EA, Stansbrey R, Gracious BL, Reed MD, Calabrese JR: Double-blind, 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44:409–417, 2005.
- Fisher L, Dixon D, Herson J, Frankowski R, Hearon M, Pearce K: Intention to treat in clinical trials. In: *Statistical Issues in Drug Research and Development*. Edited by Pearce K. New York, Marcel Dekker, 1990, pp 331–350.
- Gaffney GR, Perry PJ, Lund BC, Bever-Stille KA, Arndt S, Kuperman S: Risperidone versus clonidine in the treatment of children and adolescents with Tourette syndrome. *J Am Acad Child Adolesc Psychiatry* 41:330–336, 2002.
- Geller B, Cooper TB, Sun K, Zimmerman MA, Frazier J, Williams M, Heath J: Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance

- dependency. *J Am Acad Child Adolesc Psychiatry* 37:171–178, 1998a.
- Geller B, Warner K, Williams M, Zimmerman B: Prepubertal and young adolescent bipolarity versus ADHD: Assessment and validity using the WASH-U-KSADS, CBCL, and TRF. *J Affect Disord* 51:93–100, 1998b.
- Geller B, Zimmerman B, Williams M, DelBello MP, Frazier J, Beringer L: Phenomenology of prepubertal and early adolescent bipolar disorder: Examples of elated mood, grandiose behaviors, decreased need for sleep, racing thoughts, and hypersexuality. *J Child Adolesc Psychopharmacol* 12:3–9, 2002a.
- Geller B, Zimmerman B, Williams M, DelBello M, Bolhofner K, Craney J, Frazier J, Beringer L, Nickelsburg M: DSM-IV mania symptoms in a prepubertal and early adolescent BD phenotype compared to attention-deficit/hyperactive and normal controls. *J Child Adolesc Psychopharmacol* 12:11–25, 2002b.
- Gram LF, Rafaelsen OJ: Lithium treatment of psychotic children and adolescents: A controlled, clinical trial. *Acta Psychiatrica Scandinavica* 48:253–260, 1972.
- Guy W: ECDEU Assessment Manual for Psychopharmacology, Revised. Rockville (Maryland), U.S. Department of Health, Education, and Welfare, 1976.
- Hyun M, Friedman SD, Dunner DL: Relationship of childhood physical and sexual abuse to adult bipolar disorder. *Bipolar Disord* 2:131–135, 2000.
- Kafantaris V, Coletti D, Dicker R, Padula G, Kane J: Adjunctive antipsychotic treatment of adolescents with bipolar psychosis. *J Am Acad Child Adolesc Psychiatry* 40:1448–1456, 2001b.
- Kafantaris V, Coletti D, Dicker R, Padula G, Kane J: Lithium treatment of acute mania in adolescents: A large, open trial. *J Am Acad Child Adolesc Psychiatry* 42:1038–1045, 2003.
- Kafantaris V, Coletti DJ, Dicker R, Padula G, Kane JM, Pleak RR, Alvir JM: Lithium treatment of acute mania in adolescents: A placebo-controlled discontinuation study. *J Am Acad Child Adolesc Psychiatry* 43:984–993, 2004.
- Kafantaris V, Dicker R, Coletti D, Kane J: Adjunctive antipsychotic treatment is necessary for adolescents with psychotic mania. *J Child Adolesc Psychopharmacol* 11:409–413, 2001a.
- Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M: Treatment guidelines for children and adolescents with bipolar disorder: Child psychiatric workgroup on bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44:213–235, 2005.
- Kowatch R, Suppes T, Carmody T, Bucci J, Hume J, Kromelis M, Emslie G, Weinberg W, Rush A: Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescent with BD. *J Am Acad Child Adolesc Psychiatry* 39:713–720, 2000.
- Kowatch R, Sethuraman G, Hume J, Kromelis M, Weinberg W: Combination pharmacotherapy in children and adolescents with BD. *Biol Psychiatry* 53:978–984, 2003.
- Lena B: Lithium in child and adolescent psychiatry. *Arch Gen Psychiatry* 36:854–855, 1979.
- Leverich GS, McElroy SL, Suppes T, Keck PE, Jr, Denicoff KD, Nolen WA, Alshuler, Rush AJ, Kupka R, Frye MA, Autio KA, Post RM: Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biol Psychiatry* 51:288–297, 2002.
- McClellan J, Werry J: Evidence-based treatments in child and adolescent psychiatry: An inventory. *J Am Acad Child Adolesc Psychiatry* 42:1388–1400, 2003.
- McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, Arnold LE, Lindsay R, Nash P, Hollway J, McDougle CJ, Posey D, Swiezy N, Kohn A, Scahill L, Martin A, Koenig K, Volkmar F, Carroll D, Lancor A, Tierney E, Ghuman J, Gonzalez NM, Grados M, Vitiello B, Ritz L, Davies M, Robinson J, McMahon D: Research units on pediatric psychopharmacology autism network: Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 347:314–321, 2002.
- McKnew DH, Cytryn L, Buchsbaum MS, Hamovit J, Lamour M, Rapoport JL, Gershon ES: Lithium in children of lithium-responding parents. *Psychiatry Res* 4:171–180, 1981.
- Mota-Castillo M, Torruella A, Engels B, Perez J, Dedrick C, Gluckman M: Valproate in very young children: An open case series with a brief follow-up. *J Affect Disord* 67:193–197, 2001.
- Pavuluri MN, Henry DW, Devineni B, Carbray JA, Naylor MW, Janicak PG: A pharmacotherapy algorithm for stabilization and maintenance for pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 43:859–867, 2004a.
- Pavuluri MN, Henry DW, Naylor M, Carbray J, Janicak PG: Divalproex sodium in pediatric mixed mania: A six-month, open-label trial. *Bipolar Disord* 7:266–273, 2005.
- Pavuluri MN, Henry DW, Naylor M, Sampson G, Carbray J, Janicak PG: A prospective trial of combination therapy of risperidone with lithium or divalproex sodium in pediatric mania. *J Affect Disord* 82(Suppl 1):103–111, 2004b.
- Pavuluri MN, Janicak PG: Handbook of Pharmacotherapy: A Life Span Approach. Baltimore (Maryland)/Philadelphia, (Pennsylvania), Lippincott Williams & Wilkins, 2004.
- Pavuluri MN, Janicak P, Carbray JA: Topiramate plus risperidone for controlling weight gain and symptoms in preschool mania. *J Child Adolesc Psychopharmacol* 12:271–273, 2002a.
- Pavuluri MN, Naylor MW, Janicak PG: Recognition and treatment of pediatric bipolar disorder. *Contemp Psychiatry* 1:1–9, 2002b.

- Pliszka SR, Lopez M, Crismon ML, Toprac MG, Hughes CW, Emslie GJ, Boemer C: A feasibility study of the children's medication algorithm project (CMAP) algorithm for the treatment of ADHD. *J Am Acad Child Adolesc Psychiatry* 42:279-287, 2003.
- Poznanski E, Grossman J, Buchsbaum Y, Banegas M, Freeman L, Gibbons R: Preliminary studies of the reliability and validity of the children's depression rating scale. *J Am Acad Child Psychiatry* 23:191-197, 1984a.
- Poznanski E, Israel M, Grossman J: Hypomania in a four year old. *J Am Acad Child Psychiatry* 23:105-110, 1984b.
- Scheffer R, Kowatch R, Carmody T, Rush J: Randomized, placebo-controlled trial of dextroamphetamine for symptoms of comorbid ADHD in pediatric bipolar disorder. *Am J Psychiatry* 162:58-64, 2005.
- Segal J, Berk M, Brook S: Risperidone compared with both lithium and haloperidol in mania: A double-blind, randomized, controlled trial. *Clin Neuropharmacol* 21:176-180, 1998.
- Shaffer D, Gould M, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S: Children's global assessment scale (C-GAS). *Arch Gen Psychiatry* 40:1228-1231, 1983.
- Small JG, Klapper MH, Milstein V, Kellams JJ, Miller MJ, Marhenke JD, Smal IF: Carbamazepine compared with lithium in the treatment of mania. *Arch Gen Psychiatry* 48:915-921, 1991.
- Snyder R, Turgay A, Aman M, Binder C, Fisman S, Carroll A: Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage IQs. *J Am Acad Child Adolesc Psychiatry* 41:1026-1036, 2002.
- Soutullo CA, DelBello MP, Ochsner JE, McElroy SL, Taylor SA, Strakowski SM, Keck PE, Jr: Severity of bipolarity in hospitalized manic adolescents with history of stimulant or antidepressant treatment. *J Affect Disord* 70:323-327, 2002.
- Spearing M, Post R, Leverich G, Brandt D, Nolen W: Modification of the Clinical Global Impressions (CGI) scale for use in bipolar illness (BP): The CGI-BP. *Psychiatry Res* 73:159-171, 1997.
- Strober M, De Antonio M, Schmidt-Lackner S, Freeman R, Lampert C, Diamond J: Early childhood attention-deficit/hyperactivity disorder predicts poorer response to acute lithium therapy in adolescent mania. *J Affect Disord* 51:145-151, 1998.
- Strober M, Morrell W, Burroughs J, Lampert C, Danforth H, Freeman R: A family study of bipolar I disorder in adolescence: Early onset of symptoms linked to increased family loading and lithium resistance. *J Affect Disord* 15:255-268, 1988.
- Task Force on Research Diagnostic Criteria: Infancy and Preschool: Research diagnostic criteria for infants and preschool children: The process and empirical support. *J Am Acad Child Adolesc Psychiatry* 42:1504-1512, 2003.
- Tuzun U, Zoroglu S, Savas H: A 5-year-old boy with recurrent mania successfully treated with carbamazepine. *Psychiatry Clin Neurosci* 56:589-591, 2002.
- Weissman M, Wickramaratne P, Adams P, Wolk S, Verdelli H, Olfson M: Brief screening for the family history: The Family History Screen. *Arch Gen Psychiatry* 57:675-682, 2000.
- Wilens T, Biederman J, Brown S, Monuteaux M, Prince J, Spencer T: Patterns of psychopathology and dysfunction in clinically referred preschoolers. *J Dev Behav Pediatr* 23(Suppl 1):S31-S36, 2002.
- Young R, Biggs J, Ziegler V, Meyer D: A rating scale for mania: Reliability, validity, and sensitivity. *Br J Psychiatry* 133:429-435, 1978.

Address reprint requests to:
 Mani N. Pavuluri, M.D., Ph.D.
 Pediatric Mood Disorders Program
 Department of Psychiatry
 University of Illinois at Chicago
 912 South Wood Street (M/C 913)
 Chicago, IL 60612-7347

E-mail: mpav@uic.edu

This article has been cited by:

1. Christoph U. Correll , John M. Kane . 2007. One-Year Incidence Rates of Tardive Dyskinesia in Children and Adolescents Treated with Second-Generation Antipsychotics: A Systematic Review. *Journal of Child and Adolescent Psychopharmacology* **17**:5, 647-656. [[Abstract](#)] [[PDF](#)] [[PDF Plus](#)]