ONLINE FIRST

A Randomized Controlled Trial of Risperidone, Lithium, or Divalproex Sodium for Initial Treatment of Bipolar I Disorder, Manic or Mixed Phase, in Children and Adolescents

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Context: There was a paucity of comparative pharmacological research for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents.

Objective: To investigate which medication to administer first to antimanic medication–naive subjects.

Design, Setting, and Participants: The Treatment of Early Age Mania (TEAM) study recruited 6- to 15-year-old children and adolescents with *DSM-IV* bipolar I disorder (manic or mixed phase) at 5 US sites from 2003 to 2008 into a controlled, randomized, no-patient-choice, 8-week protocol. Blinded, independent evaluators conducted all baseline and end-point assessments.

Interventions: Subjects received a titrated schedule of lithium, divalproex sodium, or risperidone. Medications were increased weekly only if there was inadequate response, and no dose-limiting adverse effects, to maximum doses of lithium carbonate (1.1-1.3 mEq/L), divalproex sodium (111-125 µg/mL), and risperidone (4-6 mg).

Main Outcome Measures: Primary outcome measures were the Clinical Global Impressions for Bipolar Illness Improvement–Mania and the Modified Side Effects Form for Children and Adolescents.

Results: There were 279 antimanic medication–naive subjects (mean [SD] age, 10.1 [2.8] years; 50.2% female) who had the following characteristics: 100% elated mood and/or grandiosity, 77.1% psychosis, 97.5% mixed mania, 99.3% daily rapid cycling, and mean (SD) mania duration of 4.9 (2.5) years. The mean (SD) titrated lithium level was 1.09 (0.34) mEq/L, and the mean (SD) divalproex sodium level was 113.6 (23.0) µg/mL. The mean (SD) titrated risperidone dose was 2.57 (1.21) mg. Higher response rates occurred with risperidone vs lithium (68.5% vs 35.6%; $\chi^2_1=16.9$, $P<.001$) and vs divalproex sodium (68.5% vs 24.0%; $\chi^2_1=28.3$, $P<.001$). Response to lithium vs divalproex sodium did not differ. The discontinuation rate was higher for lithium than for risperidone ($\chi^2_1=6.4$, $P=.011$). Increased weight gain, body mass index, and prolactin level occurred with risperidone vs lithium ($F_{1,212}=45.5$, $P<.001$; $F_{1,212}=39.1$, $P<.001$; and $F_{1,213}=191.4$, $P<.001$, respectively) and vs divalproex sodium ($F_{1,212}=34.7$, $P<.001$; $F_{1,212}=45.3$, $P<.001$; and $F_{1,213}=209.4$, $P<.001$, respectively). The thyrotropin level increased in subjects taking lithium ($t_{62}=11.3$, $P<.001$).

Conclusions: Risperidone was more efficacious than lithium or divalproex sodium for the initial treatment of childhood mania but had potentially serious metabolic effects.

Trial Registration: clinicaltrials.gov Identifier: NCT00057681

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CHILDHOOD MANIA IS A SERIOUSLY impairing, often psychotic illness with a chronic natural history that continues into adulthood and has increased risks of substance use disorders and suicidality.[1-6] These clinical phenomena warrant rigorous intervention and may be, in part, responsible for the recent dramatic increase in use of antipsychotic medications for child psychiatry outpatients.[7] In spite of marked metabolic effects of antipsychotic medications in children[8] and the consequent need for comparative pharmacological research, there is a dearth of such studies.[9]

Especially in comparison with the wealth of investigations of the 3 main classes (antipsychotic, anticonvulsant, and lithium) of antimanic agents for adults with mania, there are few randomized trials for child mania. Several multisite random-

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ized clinical trials of atypical antipsychotics found efficacy for olanzapine,[10] risperidone,[11] and aripiprazole[12] compared with placebo for acute treatment of adolescent mania, but these studies did not include children younger than 10 years or comparative medications. Two multisite randomized clinical trials of anticonvulsants, including one of divalproex sodium extended release[13] and one of oxcarbazapine,[14] had negative findings.

The Treatment of Early Age Mania (TEAM) study (http://www.nimh.nih.gov/trials/datasets/nimh-policy-for-distribution-of-data.shtml) had 2 components to address 2 main questions: (1) which medication to give first to antimanic medication–naive subjects, and (2) if the first medication failed, which medication to add on for partial responders or switch to for nonresponders, which will be reported separately. To the best of our knowledge, the TEAM study is the first randomized, controlled, comparative drug study of 3 major classes of antimanic medications in children aged 6 years or older.

METHODS

The TEAM study's main component was a controlled, randomized (1:1:1), no-patient-choice, 8-week parallel comparison of risperidone, lithium carbonate, and divalproex sodium in antimanic medication–naive subjects. Five sites participated during the period from 2003 to 2008: the Children's National Medical Center in Washington, DC; the Johns Hopkins Medical Institutions in Baltimore, Maryland; the University of Pittsburgh in Pennsylvania; the University of Texas Medical Branch in Galveston and the University of Texas Southwestern in Dallas; and Washington University in St Louis, Missouri.

The study was funded by the National Institute of Mental Health (NIMH). Research clinicians obtained consent from primary caretakers and assent from children. The human studies committee at each site approved the protocols, and the NIMH Data Safety and Monitoring Board monitored the study conduct. During the first 2 years of the study, Abbott supplied Depakote but had no other input and no knowledge of the study data or conduct. All other study medications were purchased by the sites' pharmacies using the same procedures used for other purchases, which obviated bias by purchase method. Because of subjects' severity, including suicidal children if they could be managed as outpatients, an open paradigm, rather than a placebo-controlled design, was selected, to enhance recruitment feasibility.

STUDY POPULATION

Participants were outpatients 6.0 to 15.11 years old with a *DSM-IV* diagnosis of bipolar I disorder, manic or mixed episode, for at least 4 consecutive weeks immediately preceding baseline, with a Children's Global Assessment Scale (CGAS)[15] score of 60 or less at baseline and in good physical health. Cooccurring attention-deficit hyperactivity, oppositional defiant, and conduct disorders were allowed because these are common comorbidities in childhood mania.[16-18] Suicidal ideation was allowed if there was no imminent risk. Exclusion criteria were an IQ of less than 70, a lifetime history of schizophrenia, pervasive developmental disorder or major medical or neurological disease, substance use dependency, alcohol or drug abuse within the past 4 weeks, pregnancy, sexually active and not using contraceptives, or nursing. Other psychotropics (eg, atomoxetine hydrochloride) and medications associated with psychiatric symptoms were not permitted. Stable (≥3 previous months) maintenance methylphenidate and amphetamine preparations (total daily dose equivalent to ≤60 mg methylphenidate), verified by pharmacy/physician records, and allergy/asthma medications were allowed, to mimic usual clinical practice. No stimulant dose adjustment was allowed during protocol. Antidepressants were tapered during the first week of study to avoid risk of increased mania symptoms.[19] Subjects required no history of receiving study psychotropics or their equivalents. All medication histories were verified by physician and/or pharmacy records to enhance interview accuracy.

RECRUITMENT AND SCREENING

Subjects were recruited from media advertisements and clinical referrals. Initial telephone screenings excluded children with obvious exclusion criteria. Physician and pharmacy records to document medication history were obtained during screenings. As shown in **Figure 1**, of 5671 subjects screened, 712 were eligible for baseline assessment. Of the 712 subjects eligible for baseline assessment, 379 were eligible for 1 of the 2 components of the study and were assigned to either medication-naive (n=290) or partial/nonresponder categories (n=89). No potential subject refused to be videotaped.

STUDY INTERVENTION

Table 1 details titration schedules for twice-a-day dosing, which included lithium at 1.1 to 1.3 mEq/L (to convert to millimoles per liter, multiply by 1.0), divalproex sodium at 111 to 125 μg/mL (to convert to micromoles per liter, multiply by 6.934), and risperidone at 4 to 6 mg. Lithium and divalproex sodium blood levels were obtained 10 to 12 hours after the dose and were titrated (Table 1) using weekly Clinical Global Impressions for Bipolar Illness Improvement–Mania (CGI-BP-IM) and adverse effects scores. Subjects with a weight gain that was more than 15% of their baseline weight and with a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) above the 75th percentile were discontinued from the study. Only 1 subject was discontinued for this reason. One other subject had a dose-limiting weight gain but mistakenly was not discontinued. Subjects were begun at low doses, and doses were only increased if a child had minimal or no response (Table 1) and no dose-limiting adverse effects. Allowing high titrated blood levels ensured a comprehensive trial of lithium and divalproex sodium.

Weekly pill minders[20] were used to dispense medication and were brought to each visit for pill counts. Ten doses of chlorpromazine at 25 mg each were allowed as rescue medications during weeks 1 to 4.

RANDOMIZATION AND BLINDING

Randomization was stratified by age group (6-12 vs 13-15 years) and by the presence or absence of the following characteristics: mixed mania, psychosis, and daily rapid cycling. A separate random list of medication assignments was created for each site based on these stratifiers. Age was selected because of data showing differences in response for multiple medications by age group.[21,22] Effects of mixed mania, psychosis, and rapid cycling were used because of the differential response in some studies of adults.[23] Although similar data are unavailable for children, it seemed wise to stratify by these variables, to avoid the unlikely but statistically problematic situation of confounding results due to unequal randomization. The ranuni function in the SAS version 8.1 statistical software package (SAS Institute Inc) was used to create random lists of the 3 medications for each combination of the stratifying variables at each

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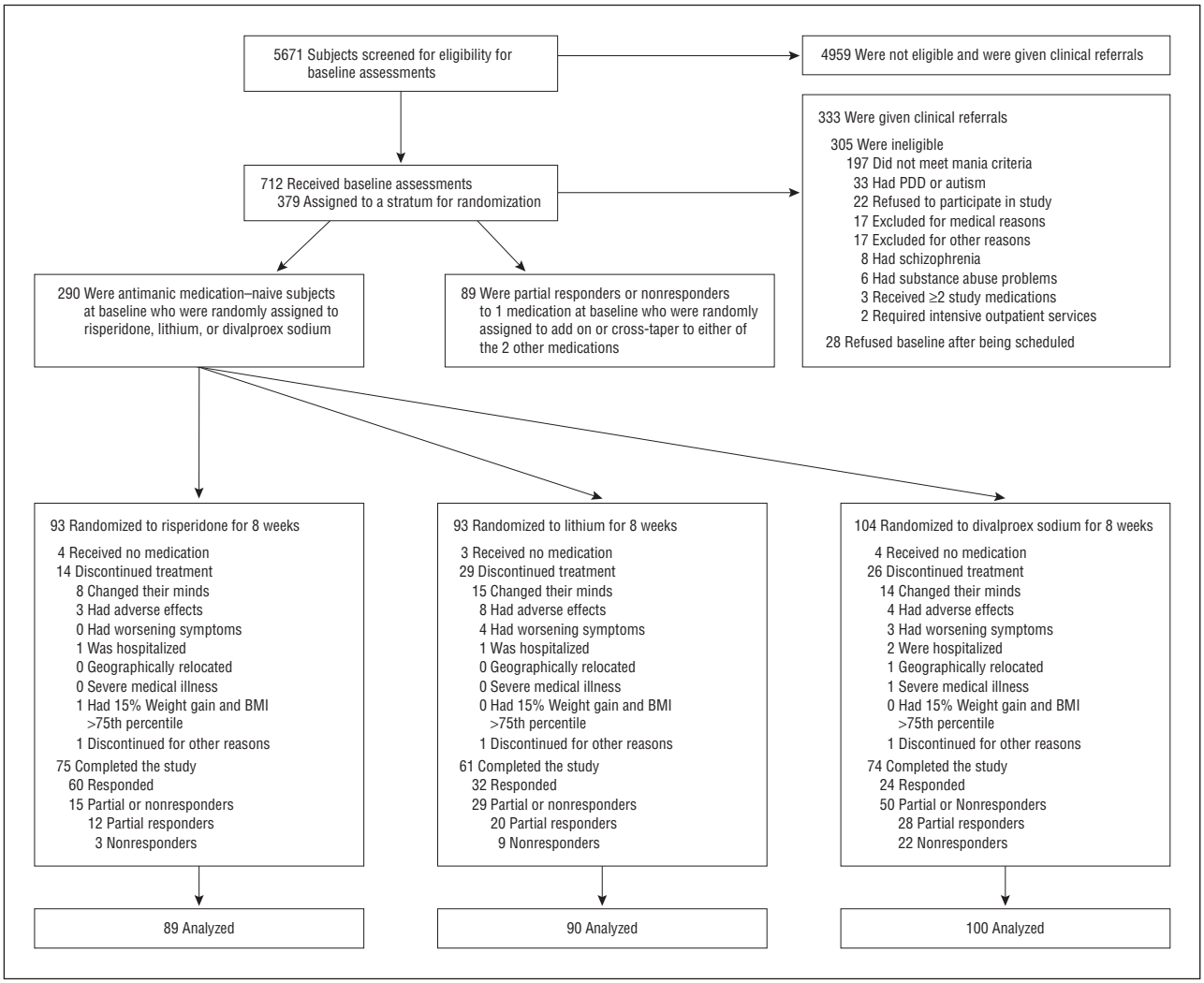

Figure 1. Flowchart of subjects (6-15 years of age) in the Treatment of Early Age Mania (TEAM) study that investigated which medication to administer first to antimanic medication–naive subjects. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); PDD, pervasive developmental disorder.

site.[24] When subjects were randomly assigned, the randomized medication was determined by selecting the next available entry in the list corresponding to the subject's stratifying variables and site. Randomization was performed at the coordinating site, and a form identifying the randomized medication was e-mailed to the site's nonblinded staff members.

Patients, family members, and treating clinicians were aware of treatment assignment. Independent evaluators (IEs) who were blinded to medication status administered baseline and end-point assessments. Masking of the treatment assignment to the IEs was strictly enforced by using staff who were totally uninvolved with the subjects' treatment. Families were instructed not to reveal either the medication or adverse effects to the blinded end-point raters. Separate, nonblinded interviewers conducted the weekly assessments.

STUDY ASSESSMENTS

The Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) *DSM-IV* mania diagnosis is made by defining the onset, offset, and severity of each mania symptom. The WASH-U-KSADS was selected because it is widely used across NIMH-funded and manufacturer-sponsored research on child mania, at multiple sites, and thus allows comparability across studies. The WASH-U-KSADS was used in the NIMH-funded multisite Pediatric Bipolar Collaborative Mood Stabilizer Trial (NCT00221429) and in manufacturer-sponsored multisite pediatric mania Depakote studies.[13,14] It is a comprehensive, semistructured interview administered by highly trained professionals. Symptoms only count if they are pervasive, persistent, and severe and cause definite clinical impairment, and ratings had to be accompanied by convincing documentation.[25] Geller et al[26] provide examples that are developmentally possible for children. Examples of grandiose child behaviors include a 9-year-old student who told the principal to fire a teacher he did not like and a 6-year-old child who started a business by going door-to-door selling beer from the family refrigerator.

To receive a diagnosis of mania, a sufficient number of mania symptoms of moderate or greater severity must occur in overlapping time frames. For mania symptoms to be considered present, the level of severity had to be 4 or greater (moderate-extreme), consistent with clinically meaningful impairment. Mixed mania required meeting *DSM-IV* criteria for both mania and depressive disorders in overlapping time frames. Other diagnoses were considered present if they co-occurred within the same time frame as mania. Daily rapid cycling included 4 or more hours each day of fitting all *DSM-IV* mania

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Table 1. Titration Schedule for the TEAM Study

Weight at Visit	Dosage: Risperidone	Dosage: Lithium	Dosage: Divalproex Sodium
Dispensing visit			
<25 kg	0.25 mg qHS for 2 d, then 0.25 mg twice a day	150 mg qHS for 2 d, then 150 mg twice a day	125 mg qHS for 2 d, then 125 mg twice a day
25-50 kg	0.25 mg twice a day for 2 d, then 0.5 mg twice a day	150 mg twice a day x 2 d, then 300 mg twice a day	250 mg qHS for 2 d, then 125/250 mg
>50 kg	0.25 mg twice a day for 2 d, then 0.5 mg twice a day	300 mg twice a day for 2 d, then 300 mg AM/600 mg PM	250 mg qHS for 2 d, then 250 mg twice a day
All weights at week 1	Maintain dispensing-visit dose	Adjust dose to 0.8 mEq/L	Adjust dose to 75 μg/mL
Week 2	**Only If CGI-BP-IM>2 and Current Dose Tolerated, Increase as Instructed Below**		
<25 kg	Increase to 0.5 mg twice a day	Adjust to 0.9-1.0 mEq/L	Adjust to 100-110 μg/mL
25-50 kg	Increase to 1.0 mg twice a day	Adjust to 0.9-1.0 mEq/L	Adjust to 100-110 μg/mL
>50 kg	Increase to 1.0 mg twice a day	Adjust to 0.9-1.0 mEq/L	Adjust to 100-110 μg/mL
All weights at week 3	Maintain week-2 dose	Maintain week-2 dose	Maintain week-2 dose
Week 4	**Only If CGI-BP-IM>1 and Current Dose Tolerated, Increase as Instructed Below**		
<25 kg	Increase to 1.0 mg twice a day	Adjust to 1.1-1.3 mEq/L	Adjust to 111-125 μg/mL
25-50 kg	Increase to 1.5 mg twice a day	Adjust to 1.1-1.3 mEq/L	Adjust to 111-125 μg/mL
>50 kg	Increase to 2.0 mg twice a day	Adjust to 1.1-1.3 mEq/L	Adjust to 111-125 μg/mL
All weights at week 5	Maintain week-4 dose	Maintain week-4 dose	Maintain week-4 dose
Week 6	**Only If CGI-BP-IM>1 and Current Dose Tolerated, Increase as Instructed Below**		
<25 kg	Increase to 2.0 mg twice a day	Maintain 1.1-1.3 mEq/L	Maintain 111-125 μg/mL
25-50 kg	Increase to 2.0 mg/3.0 mg	Maintain 1.1-1.3 mEq/L	Maintain 111-125 μg/mL
>50 kg	Increase to 3.0 mg twice a day	Maintain 1.1-1.3 mEq/L	Maintain 111-125 μg/mL
All weights at week 7	Maintain week-6 dose	Maintain week-6 dose	Maintain week-6 dose
All weights at week 8	End of study or dispensing visit for 2nd 8-week dose	End of study or dispensing visit for 2nd 8-week dose	End of study or dispensing visit for 2nd 8-week dose

Abbreviations: CGI-BP-IM, Clinical Global Impressions for Bipolar Illness Improvement–Mania; qHS, every night at bedtime; TEAM, Treatment of Early Age Mania.

SI conversion factors: To convert lithium to millimoles per liter, multiply by 1.0; and to convert divalproex sodium to micromoles per liter, multiply by 6.934.

criteria. There could be times during the day when not all mania criteria were met.

Primary caretakers and children were evaluated by different independent raters to avoid potential bias from knowing the responses of either caretaker or child informant within a dyad. Parent or guardian and child ratings were combined using the most severe rating from either, consistent with Bird et al.[27] For children aged 6 years, time frames were only from the caretaker. For children aged 7 years or older, time frames were obtained from children by using anchors (eg, what grade they were in when symptoms began, before or after birthdays and holidays).

All baseline and end-point WASH-U-KSADS interviews were videotaped and independently rated by the coordinating site's IEs. Discrepancies between data collection and coordinating site ratings were resolved via electronic and telephonic communications. Only subjects who fit by consensus of IEs at both data collection and coordinating sites were enrolled.

The Children's Global Assessment Scale (CGAS)[28] provided a severity measure based on functioning in home, school, and social domains. On this scale, a score of 60 or less signifies clinical impairment. Research clinicians and IEs trained for a week at Washington University in St Louis to achieve interrater reliability of 90% for mania symptoms and psychiatric diagnoses on the WASH-U-KSADS.[25]

STUDY OUTCOME MEASURES

The primary outcome measure was the CGI-BP-IM.[29] Ratings of 1 or 2 (very much or much improved, respectively) counted for response. Independent evaluators' judgment of parent and child assessments determined the CGI-BP-IM scores. The secondary outcome measure was the K-SADS Mania Rating Scale (KMRS),[30] which is a continuous measure of mania symptom severity.

All assessment times included the Modified Side Effects Form for Children and Adolescents,[31] modified for lithium toxicity, and the Modified Abnormal Involuntary Movement Scale (AIMS).[32] The Modified AIMS included measures of dystonia and akathisia and instructions for examining cogwheeling and tongue dyskinesias in children. Laboratory measures were nonfasting.

STATISTICAL ANALYSES

Of the 290 subjects who fit the study criteria and were enrolled, 11 randomly assigned subjects did not appear for the visit to dispense medication. Therefore, these subjects could not have known what medication they would have received. These 11 subjects were excluded from the intent-to-treat sample (Figure 1). The intent-to-treat sample included all subjects (N=279) who had medication dispensed and thus knew what medication they had been assigned to. Seven subjects in the intent-to-treat sample were dispensed medication but did not appear for the week-1 assessment. Therefore, their reason for discontinuing treatment could be biased by their medication assignment. To account for this, sensitivity analyses were conducted with and without these 7 subjects. The planned sample size was 216 medication-naive subjects (72 randomly as-

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signed to each medication). This sample size of 216 provides an effect size of 0.60 at $\alpha = .01$ and 83% power. The actual sample sizes were 89 subjects in the risperidone group, 90 subjects in the lithium group, and 100 subjects in the divalproex sodium group, resulting in 80% power at $\alpha = .01$ to detect an effect size of 0.51 for comparisons between the risperidone and lithium groups and an effect size of 0.50 for comparisons between the risperidone and divalproex sodium groups or between the lithium and divalproex sodium groups.

Baseline demographic and mania characteristics, comorbid diagnoses, and discontinuation rates were compared by randomized medication group using general linear models for continuous variables and logistic regression for dichotomous variables. To compare response by randomized medication group, a logistic regression model with end-point CGI-BP-IM response status as the dependent variable was conducted. Subjects who discontinued treatment before the end-point assessment were considered nonresponders. Independent variables in the logistic regression model included age, sex, socioeconomic status, psychosis, CGI-BP Severity–Mania (CGI-BP-SM) score, site, stimulant medication use, allergy/asthma medication use, and randomized medication used.

Secondary analyses included a general linear model with end-point KMRS score as the dependent variable. For subjects who discontinued treatment before the end-point assessment, the KMRS score at the last completed assessment was used for outcome, so this analysis utilized a last observation carried forward approach. Independent variables in the model were the same as those in the model of CGI-BP-IM, except that baseline KMRS score replaced baseline CGI-BP-SM score as a covariate.

Logistic regression models of the end-point CGAS response and of the presence or absence of *DSM-IV* mania at end point were used to compare randomized medication groups. The CGAS response was defined as a CGAS score of greater than 60, and subjects without a diagnosis of mania at end point were considered responders for that analysis. Subjects who discontinued treatment before the end-point assessment were considered nonresponders. For the CGAS and absence of mania analyses, baseline CGAS score and baseline KMRS score, respectively, were included as covariates instead of baseline CGI-BP-SM score. The Mantel-Haenszel test was also conducted for end-point CGAS response and for presence or absence of *DSM-IV* mania at end point. These tests controlled for site.

Using a paired *t* test, we compared the baseline and week-8 laboratory measures for subjects who completed the week-8 assessment in each randomized medication group. Using general linear models with contrast statements for the pairwise medication group comparisons, we compared changes in laboratory measures between baseline and week 8 in the 3 randomized medication groups for all subjects who completed the week-8 assessment. Because laboratory data were only collected at baseline and at end point, analyses could only be conducted for subjects who completed the end-point assessment.

Adverse effects were considered present if the severity level was a 2 or 3 (moderate or severe, respectively). Adverse effects present at baseline and for at least 1 week during weeks 1 to 8 were compared separately for each randomized medication group by use of the McNemar χ^2 test for paired categorical data and were compared in the 3 medication groups by use of logistic regression with contrast statements for the pairwise medication group comparisons. Modified AIMS scores were broken down into 3 categories (≥ 1, ≥ 2, and ≥ 3) at baseline and at any week during weeks 1 to 8. These categories were compared between baseline and during weeks 1 to 8 for each randomized medication group by use of the McNemar χ^2 test. Comparisons between randomized medication groups were made by use of logistic regression with contrast statements for the pairwise medication group comparisons.

The Bonferroni method was used to account for multiple comparisons of the primary outcome measure. The corrected significance level was $P < .017$. All analyses were conducted with SAS version 9.2 statistical software (SAS Institute Inc).

RESULTS

RECRUITMENT SOURCE, SUBJECT FLOW, AND DISCONTINUATION RATE

Recruitment by source was as follows: 140 subjects (50.2%) were recruited from media advertisements (radio, print, television, Internet, brochure, or on-hold line), 109 (39.1%) from a physician at a clinic or in private practice, and 30 (10.7%) from other sources (eg, a teacher or a parent of another subject). There was no significant difference in CGI-BP-IM response by referral source ($\chi^2_2 = 1.4$, $P = .50$). The only baseline variable that was significantly different by referral group was baseline CGI-BP-SM score. "Media" had a lower mean (SD) baseline CGI-BP-SM score than "other" (5.89 [0.60] vs 6.23 [0.63]; $F_{1,276} = 7.9$, $P = .005$).

Figure 1 presents overall flow of subjects in the study. Of the 279 randomly assigned medication-naive subjects, 24.7% discontinued treatment (eTable 1). The discontinuation rate was significantly higher for subjects randomly assigned to the lithium group than for subjects randomly assigned to the risperidone group (32.2% vs 15.7%; $\chi^2_1 = 6.4$, $P = .011$). The discontinuation rates did not differ between the risperidone and divalproex sodium groups (15.7% vs 26.0%; $\chi^2_1 = 2.9$, $P = .09$) or between the lithium and divalproex sodium groups (32.2% vs 26.0%; $\chi^2_1 = 0.9$, $P = .35$).

SUBJECT CHARACTERISTICS

Table 2 shows baseline demography, mania characteristics, and comorbid disorders of the subjects by randomized medication group. In the TEAM study, mania was further delineated from attention-deficit/hyperactivity disorder by 100% of subjects having elated mood and/or grandiose behaviors, neither of which are diagnostic criteria in *DSM-IV* disruptive disorders.[5]

MEDICATION TITRATION AND COMPLIANCE

The mean (SD) titrated lithium blood level was 1.09 (0.34) mEq/L, the mean (SD) titrated divalproex sodium blood level was 113.6 (23.0) μg/mL, and the mean (SD) titrated risperidone dose was 2.57 (1.21) mg. The blood levels for 7.0% of 529 blood samples in the lithium group and for 7.5% of 655 blood samples in the divalproex sodium group were obtained outside of the 10- to 12-hour postdose window, but these levels were not significantly different from those within the window. There was no significant difference in percentage of pills taken between groups (95.8% for risperidone, 94.7% for lithium, and 97.1% for divalproex sodium).

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Table 2. Baseline Demography, Mania Characteristics, and Comorbid Diagnoses of Children and Adolescents in the TEAM Study[a]

Characteristic	Subjects, No. (%)			
	Total (n=279)	Risperidone (n=89)	Lithium (n=90)	Divalproex Sodium (n=100)
Age, mean (SD), y	10.1 (2.8)	11.0[b] (3.0)	9.7 (2.7)	9.7 (2.4)
Socioeconomic status,[c] mean (SD), scale	3.7 (1.0)	3.6 (1.1)	3.7 (1.0)	3.8 (0.9)
Age group, y				
6.0-12.11	218 (78.1)	57 (64.0)	74 (82.2)	87 (87.0)
13.0-15.11	61 (21.9)	32 (36.0)[d]	16 (17.8)	13 (13.0)
Sex				
Female	140 (50.2)	47 (52.8)	37 (41.1)	56 (56.0)
Male	139 (49.8)	42 (47.2)	53 (58.9)	44 (44.0)
Pubertal status				
Prepubertal	177 (63.4)	50 (56.2)	58 (64.4)	69 (69.0)
Pubertal	102 (36.6)	39 (43.8)	32 (35.6)	31 (31.0)
Race				
White	203 (72.8)	60 (67.4)	66 (73.3)	77 (77.0)
Black	54 (19.4)	21 (23.6)	17 (18.9)	16 (16.0)
Hispanic	6 (2.2)	2 (2.2)	3 (3.3)	1 (1.0)
Other	16 (5.7)	6 (6.7)	4 (4.4)	6 (6.0)
Subjects by site				
CNMC	68 (24.4)	24 (27.0)	22 (24.4)	22 (22.0)
JHMI	50 (17.9)	18 (20.2)	15 (16.7)	17 (17.0)
PITT	39 (14.0)	15 (16.9)	15 (16.7)	9 (9.0)
UTMB/UTSW	59 (21.1)	16 (18.0)	19 (21.1)	24 (24.0)
WASHU	63 (22.6)	16 (18.0)	19 (21.1)	28 (28.0)
Mania characteristics, mean (SD)				
Mania episode onset, y	5.2 (2.6)	5.8 (2.9)	5.0 (2.7)	5.0 (2.2)
Mania episode duration, y	4.9 (2.5)	5.2 (2.7)	4.8 (2.6)	4.7 (2.4)
Lifetime mania episodes, No.	1.01 (0.08)	1.01 (0.11)	1.00 (0.00)	1.01 (0.10)
Lifetime MDD episodes, No.	1.06 (0.26)	1.04 (0.21)	1.07 (0.25)	1.08 (0.31)
CGAS score	39.1 (6.2)	39.1 (6.6)	38.9 (6.2)	39.2 (5.8)
CGI-BP-SM score	6.0 (0.6)	6.0 (0.6)	6.1 (0.6)	6.0 (0.6)
KMRS score	43.9 (6.2)	43.4 (6.2)	44.4 (7.1)	43.9 (5.3)
First mania episode	277 (99.3)	88 (98.9)	90 (100.0)	99 (99.0)
Elated mood and/or grandiosity	279 (100.0)	89 (100.0)	90 (100.0)	100 (100.0)
Elated mood	266 (95.3)	83 (93.3)	86 (95.6)	97 (97.0)
Grandiosity	253 (90.7)	83 (93.3)	79 (87.8)	91 (91.0)
Mixed mania	272 (97.5)	87 (97.8)	88 (97.8)	97 (97.0)
Psychosis[e]	215 (77.1)	71 (79.8)	64 (71.1)	80 (80.0)
Daily rapid cycling[f]	277 (99.3)	87 (97.8)	90 (100.0)	100 (100.0)
Suicidality	108 (38.7)	40 (44.9)	29 (32.2)	39 (39.0)
Nonstudy treatment during study				
Tapered from antidepressant	27 (9.7)	9 (10.1)	8 (8.9)	10 (10.0)
Preprotocol, stable stimulant medication	90 (32.3)	27 (30.3)	31 (34.4)	32 (32.0)
Allergy/asthma medication	55 (19.7)	16 (18.0)	13 (14.4)	26 (26.0)
Rescue chlorpromazine	9 (3.2)	2 (2.2)	1 (1.1)	6 (6.0)
Preprotocol, stable psychosocial intervention	23 (8.2)	7 (7.9)	7 (7.8)	9 (9.0)

(Continued)

OUTCOME

Figure 2 shows comparisons of end-point CGI-BP-IM response rates by medication. Subjects treated with risperidone had a significantly higher response rate than those treated with lithium (68.5% [n=61] vs 35.6% [n=32]; χ^2_1=16.9, $P<.001$) and those treated with divalproex sodium (68.5% [n=61] vs 24.0% [n=24]; χ^2_1=28.3, $P<.001$). There was no significant difference in response rate in the lithium vs divalproex sodium pairwise comparison.

Pairwise medication group comparisons of end-point response rates for CGAS and presence or absence of *DSM-IV* mania and pairwise medication group comparisons of final KMRS scores are shown in eTable 2. The mean (SD) KMRS scores were significantly lower in subjects treated with risperidone than in those treated with lithium (16.4 [10.2] vs 26.2 [12.7]; $F_{1,264}$=23.1, $P<.001$) or those treated with divalproex sodium (16.4 [10.2] vs 27.6 [11.3]; $F_{1,264}$=32.2, $P<.001$). Subjects treated with risperidone had significantly higher response rates than subjects treated with lithium or divalproex sodium according to CGAS (48.3% vs 26.7% [χ^2_1=8.5, P=.004] or 48.3% vs 17.0% [χ^2_1=16.5, $P<.001$], respectively) and absence of mania diagnosis (62.9% vs 41.1% [χ^2_1=6.1, P=.013] or 62.9% vs 26.0% [χ^2_1=19.1, $P<.001$], respectively).

Separate analyses of the primary outcome were conducted for 218 subjects aged 6 to 12 years and 61 sub-

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Table 2. Baseline Demography, Mania Characteristics, and Comorbid Diagnoses of Children and Adolescents in the TEAM Study[a] (continued)

Characteristic	Subjects, No. (%)			
	Total (n=279)	Risperidone (n=89)	Lithium (n=90)	Divalproex Sodium (n=100)
Comorbid diagnoses[g]				
Disruptive disorders	275 (98.6)	87 (97.8)	89 (98.9)	99 (99.0)
ADHD	259 (92.8)	81 (91.0)	82 (91.1)	96 (96.0)
Oppositional defiant disorder	251 (90.0)	77 (86.5)	85 (94.4)	89 (89.0)
Conduct disorder	44 (15.8)	17 (19.1)	15 (16.7)	12 (12.0)
Anxiety disorders	199 (71.3)	62 (69.7)	67 (74.4)	70 (70.0)
Specific phobia	158 (56.6)	49 (55.1)	53 (58.9)	56 (56.0)
Social phobia	71 (25.4)	19 (21.3)	26 (28.9)	26 (26.0)
Separation anxiety disorder	69 (24.7)	16 (18.0)	22 (24.4)	31 (31.0)
Generalized anxiety disorder	39 (14.0)	10 (11.2)	14 (15.6)	15 (15.0)
Panic attack	36 (12.9)	11 (12.4)	12 (13.3)	13 (13.0)
Obsessive-compulsive disorder	31 (11.1)	11 (12.4)	10 (11.1)	10 (10.0)
Panic disorder without agoraphobia	15 (5.4)	4 (4.5)	6 (6.7)	5 (5.0)
Sleep disorders	89 (31.9)	25 (28.1)	33 (36.7)	31 (31.0)
Nightmare disorder	72 (25.8)	19 (21.3)	25 (27.8)	28 (28.0)
Sleepwalking disorder	21 (7.5)	7 (7.9)	7 (7.8)	7 (7.0)
Sleep terror disorder	14 (5.0)	4 (4.5)	5 (5.6)	5 (5.0)
Elimination disorders	51 (18.3)	19 (21.3)	15 (16.7)	17 (17.0)
Enuresis	45 (16.1)	17 (19.1)	13 (14.4)	15 (15.0)
Encopresis	11 (3.9)	3 (3.4)	3 (3.3)	5 (5.0)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CGAS, Children's Global Assessment Scale; CGI-BP-SM, Clinical Global Impressions for Bipolar Illness Severity–Mania; CNMC, Children's National Medical Center; JHMI, Johns Hopkins Medical Institutions; KMRS, Kiddie Schedule for Affective Disorders and Schizophrenia Mania Rating Scale; MDD, major depressive disorder; PITT, University of Pittsburgh; TEAM, Treatment of Early Age Mania; UTMB/UTSW, University of Texas Medical Branch and University of Texas Southwestern; WASHU, Washington University in St Louis.

[a] Bonferroni-corrected $P=.017$.

[b] Subjects treated with risperidone were significantly older than those treated with lithium ($P=.002$) or divalproex sodium ($P<.001$).

[c] On a scale of 1 to 5, with 5 being the highest.

[d] Subjects treated with risperidone were significantly more likely to be in the age group of 13.0 to 15.11 years than were subjects treated with lithium ($P=.007$) or divalproex sodium ($P<.001$).

[e] Baseline psychosis indicates that subjects had hallucinations or delusions during part or all of their baseline mania episode. All but 2 subjects (213 of 215) with psychosis during the baseline episode were psychotic during baseline assessment.

[f] The cycle had to fit full mania criteria for at least 4 hours per day.

[g] Comorbid diagnoses were only included if at least 10 subjects had the diagnosis. The comorbid diagnoses that were present in fewer than 10 subjects were posttraumatic stress, panic with agoraphobia, agoraphobia, agoraphobia without panic, acute stress, chronic motor or vocal tic, Tourette's, transient tic, dissociative identity, dissociative amnesia, dissociative fugue, depersonalization, anorexia, and bulimia.

jects aged 13 to 15 years. Results were similar to the entire sample in both the younger age group (37 of 57 subjects [64.9%] treated with risperidone vs 26 of 74 subjects [35.1%] treated with lithium [$\chi^2_1=9.9$, $P=.002$]; 37 of 57 subjects [64.9%] treated with risperidone vs 20 of 87 subjects [23.0%] treated with divalproex sodium [$\chi^2_1=19.8$, $P<.001$]; and 26 of 74 subjects [35.1%] treated with lithium vs 20 of 87 subjects [23.0%] treated with divalproex sodium [$\chi^2_1=1.8$, $P=.17$]) and the older age group (24 of 32 subjects [75.0%] treated with risperidone vs 6 of 16 subjects [37.5%] treated with lithium [$\chi^2_1=5.2$, $P=.02$]; 24 of 32 subjects [75.0%] treated with risperidone vs 4 of 13 subjects [30.8%] treated with divalproex sodium [$\chi^2_1=8.1$, $P=.005$]; and 6 of 16 subjects [37.5%] treated with lithium vs 4 of 13 subjects [30.8%] treated with divalproex sodium [$\chi^2_1=0.8$, $P=.36$]).

For 215 subjects with psychosis, the primary outcome was similar to the primary outcome for the entire sample (49 of 71 subjects [69.0%] treated with risperidone vs 21 of 64 subjects [32.8%] treated with lithium [$\chi^2_1=14.7$, $P<.001$]; 49 of 71 subjects [69.0%] treated with risperidone vs 20 of 80 subjects [25.0%] treated with divalproex sodium [$\chi^2_1=22.7$, $P<.001$]; and 21 of 64 subjects [32.8%] treated with lithium vs 20 of 80 subjects [25.0%] treated with divalproex sodium [$\chi^2_1=0.6$, $P=.44$]). For the 64 subjects without psychosis, subjects treated with risperidone had significantly higher response rates compared with subjects treated with divalproex sodium but not compared with subjects treated with lithium, likely owing to the small sample size.

Outcomes on the primary measure were similar to the entire sample for the 90 subjects taking stimulants (18 of 27 subjects [66.7%] treated with risperidone vs 9 of 31 subjects [29.0%] treated with lithium [$\chi^2_1=7.3$, $P=.007$]; 18 of 27 subjects [66.7%] treated with risperidone vs 6 of 32 subjects [18.8%] treated with divalproex sodium [$\chi^2_1=6.3$, $P=.012$]; and 9 of 31 subjects [29.0%] treated with lithium vs 6 of 32 subjects [18.8%] treated with divalproex sodium [$\chi^2_1=0.0$, $P=.99$]) and for 189 subjects who did not take stimulants (43 of 62 subjects [69.4%] treated with risperidone vs 23 of 59 subjects [39.0%] treated with lithium [$\chi^2_1=10.9$, $P<.001$]; 43 of 62 subjects [69.4%] treated with risperidone vs 18 of 68 subjects [26.5%] treated with divalproex sodium [$\chi^2_1=19.1$, $P<.001$]; and 23 of 59 subjects [39.0%] treated with lithium vs 18 of 68 subjects [26.5%] treated with divalproex sodium [$\chi^2_1=1.0$,

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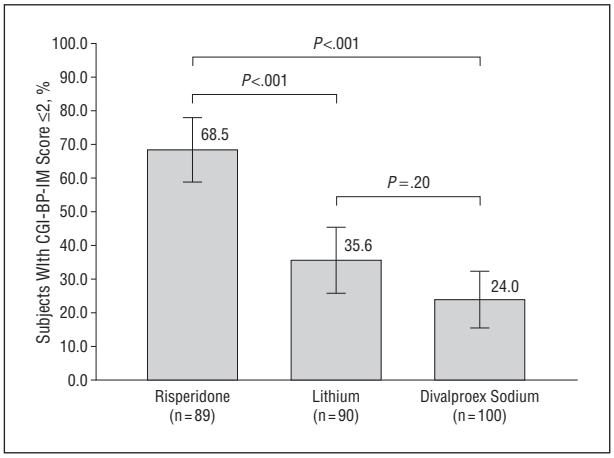

Figure 2. Comparisons of end-point Clinical Global Impressions for Bipolar Illness Improvement–Mania (CGI-BP-IM) response rates by medication. The *P* values, odds ratios (ORs), and 95% CIs were determined from logistic regression of CGI-BP-IM response, controlling for age, sex, socioeconomic status, baseline psychosis, baseline CGI-BP mania severity score, stimulant medication use, allergy/asthma medication use, and site. The error bars illustrate the 95% CIs for the proportions in the risperidone group (95% CI, 58.9%-78.2%), the lithium group (95% CI, 25.7%-45.5%), and the divalproex sodium group (95% CI, 15.6%-32.4%). For the comparison between the risperidone and lithium groups, the OR is 5.0 (95% CI, 2.3-10.9); for the comparison between the risperidone and divalproex sodium groups, the OR is 8.3 (95% CI, 3.8-18.0); and for the comparison between the lithium and divalproex sodium groups, the OR is 1.6 (95% CI, 0.8-3.5).

$P=.33$]). There were differences in CGI-BP-IM response by site, as shown in eTable 3.

ADVERSE EVENTS

Table 3 details laboratory values at baseline and week 8. The mean (SD) weight gain for subjects treated with risperidone was significantly greater than it was for subjects treated with lithium (3.31 [1.75] vs 1.42 [1.62] kg; $F_{1,212}=45.5$, $P<.001$), and the mean (SD) increase in BMI for subjects treated with risperidone was also significantly greater than it was for subjects treated with lithium (1.37 [0.77] vs 0.37 [1.24]; $F_{1,212}=39.1$, $P<.001$). The mean (SD) weight gain for subjects treated with risperidone was significantly greater than it was for subjects treated with divalproex sodium (3.31 [1.75] vs 1.67 [1.92] kg; $F_{1,212}=34.7$, $P<.001$), and the mean (SD) increase in BMI for subjects treated with risperidone was also significantly greater than it was for subjects treated with divalproex sodium (1.37 [0.77] vs 0.35 [0.82]; $F_{1,212}=45.3$, $P<.001$). There was a significant difference between the mean (SD) increased low-density cholesterol level in the risperidone group and the mean (SD) decreased low-density cholesterol level in the divalproex sodium group (2.2 [16.9] vs –6.7 [20.8] mg/dL [to convert to millimoles per liter, multiply by 0.0259]; $F_{1,210}=8.0$, $P=.005$) and between the mean (SD) decreased high-density cholesterol level in the risperidone group and the mean (SD) increased high-density cholesterol level in the divalproex sodium group (–2.3 [18.4] vs 4.1 [8.6] mg/dL [to convert to millimoles per liter, multiply by 0.0259]; $F_{1,213}=7.3$, $P=.008$). The mean (SD) thyrotropin level significantly increased between baseline and week 8 in subjects who received lithium (2.1 [1.3] vs 5.2 [2.8] mIU/L; $t_{62}=11.3$, $P<.001$). Twenty subjects had at least 1 QT interval corrected for heart rate that was greater than 440 milliseconds (9.0% of subjects treated with risperidone were in the range of 445-493 milliseconds; 10.0% of subjects treated with lithium were in the range of 443-472 milliseconds; and 3.0% of subjects treated with divalproex sodium were in the range of 442-449 milliseconds).

Table 4 shows the rates of adverse effects present at baseline and those present for at least 1 week during weeks 1 to 8 for subjects who completed at least 1 week of the study. Only adverse effects present in at least 5% of subjects who received a given medication and showing at least a 2-fold increase or decrease in prevalence during the study are included in Table 4. All adverse effects present in at least 5% of the total sample of subjects are presented in eTable 4. There were 5 subjects with reportable serious adverse effects (as defined in eTable 5). Examples of these serious adverse events included a 9-year-old male subject who was hospitalized after running into the street, despite oncoming traffic, after accusing his mother of purchasing the wrong ice cream, and an 11-year-old male subject who was hospitalized after precipitously becoming homicidal toward his brother. None of these reportable serious adverse effects were deemed related to randomized medication by the principal investigators. Suicidality significantly decreased for all medication conditions (eTable 6). There were 7 suicidal behaviors (eTable 7), but none met the definition of a reportable serious adverse effect (eTable 5).

There were no differences between groups in the use of stimulant medication (30.3% of the risperidone group, 34.4% of the lithium group, and 32.0% of the divalproex sodium group used stimulant medications), in antidepressant tapering during week 1 (10.1% of the risperidone group, 8.9% of the lithium group, and 10.0% of the divalproex sodium group), in the use of chlorpromazine as rescue medication (2.2% of the risperidone group, 1.1% of the lithium group, and 6.0% of the divalproex sodium group), or in the use of allergy/asthma medications (18.0% of the risperidone group, 14.4% of the lithium group, and 26.0% of the divalproex sodium group).

The CGI-BP-IM response rate did not differ for subjects tapered from antidepressants during week 1 vs antidepressant-free subjects (40.7% [11 of 27] vs 42.1% [106 of 252]; $\chi^2_1=0.1$, $P=.77$), for subjects continuing stable, preprotocol psychosocial interventions vs subjects not receiving psychosocial interventions (47.8% [11 of 23] vs 41.4% [106 of 256]; $\chi^2_1=0.0$, $P=.99$), or for subjects continuing stable, preprotocol stimulants vs subjects not receiving stimulants (36.7% [33 of 90] vs 44.4% [84 of 189]; $\chi^2_1=0.2$, $P=.63$). Rates of antidepressant tapering, preprotocol psychosocial interventions, and use of preprotocol stimulants by site are shown in eTables 8, 9, and 10, respectively.

There were no significant differences in discontinuation rates between medication groups due to adverse effects, as detailed in eTable 1. Findings for within–medication group comparisons of adverse effects at week of discontinuation in dropouts who changed their mind with adverse effects in completers at the mean week of discontinuation are presented in eAppendix 1. Results of sensitivity analyses are presented in eAppendix 2.

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Table 3. Laboratory Values at Baseline and Week 8

Laboratory Measure[a]	Normal Range	Laboratory Value, Mean (SD): 78 Subjects Treated With Risperidone Who Completed 8 wk: Baseline	Week 8	*P* Value
Height, cm		142.5 (17.5)	143.4 (17.5)	<.001
Weight, kg		40.7 (18.4)	44.0[b] (19.0)	<.001
BMI		19.1 (4.5)	20.4[b] (4.5)	<.001
BMI percentile		59.8 (26.1)	74.4 (18.9)	<.001
Total cholesterol, mg/dL	70-280	160.2 (35.4)	161.7 (31.9)	.51
Low-density cholesterol, mg/dL	0-175	88.0 (32.7)	90.2[c] (29.1)	.25
High-density cholesterol, mg/dL	19-110	54.0 (19.8)	51.7[d] (12.2)	.28
Triglycerides, mg/dL	28-240	113.7 (69.5)	115.9 (72.2)	.76
Blood urea nitrogen, mg/dL	5-25	11.6 (2.8)	No/S	
Creatinine, mg/dL	0.2-1.4	0.61 (0.14)	No/S	
Estimated glomerular filtration rate, mL/min		112.7 (50.8)	No/S	
Calcium, mg/dL	8-11	9.5 (0.5)	No/S	
Phosphorus, mg/dL	2.7-6.5	4.6 (0.6)	No/S	
Thyrotropin, mIU/L	0.35-7.00	1.9 (0.9)	No/S	
Total triiodothyronine, ng/dL	45-225	161.6 (35.9)	No/S	
Free thyroxine, ng/dL	0.65-3.00	1.17 (0.29)	No/S	
Prolactin, ng/mL	0-27	7.2 (4.8)	44.8[e] (26.6)	<.001
Glucose, mg/dL	60-199	84.9 (14.3)	91.3[f] (15.2)	.007
Specific gravity	1.001-1.045	1.020 (0.007)	1.019[g] (0.007)	.37
White blood cell count, $\times 10^3/\mu L$	3.0-15.5	6.4 (1.5)	No/S	
Platelet count, $\times 10^3/\mu L$	130-475	289.4 (68.8)	No/S	
Alanine aminotransferase, U/L	0-65	25.7 (17.5)	30.4 (24.1)	.014
Aspartate aminotransferase, U/L	2-65	26.8 (8.1)	28.3 (12.1)	.14
Protein, g/dL	5.5-9.0	7.35 (0.45)	7.30[h] (0.52)	.39
Albumin, g/dL	0.8-5.6	4.4 (0.3)	4.3[i] (0.3)	.015
Alkaline phosphatase, U/L	60-550	222.5 (87.4)	235.9 (90.7)	.007
Total bilirubin, mg/dL	0.1-1.3	0.46 (0.33)	0.40 (0.29)	.018
Conjugated bilirubin, mg/dL	0.0-0.4	0.10 (0.08)	0.10 (0.07)	.77
λ-Glutamyltransferase, U/L	2-55	18.3 (9.7)	17.9 (9.4)	.60
Electrocardiogram, ms				
PR	50-190	130.0 (16.9)	128.4 (16.7)	.22
QRS	50-116	82.9 (7.2)	82.9 (7.4)	.92
QTc	300-440[j]	406.9 (22.0)	410.2 (27.8)	.09
		62 Subjects Treated With Lithium Who Completed 8 wk: Baseline	**Week 8**	
Height, cm		139.8 (16.9)	141.0 (17.2)	.002
Weight, kg		40.2 (17.2)	41.6 (17.9)	<.001
BMI		19.6 (4.3)	20.0 (4.4)	.02
BMI percentile		70.3 (26.9)	70.7 (26.9)	.83
Total cholesterol, mg/dL	70-280	158.5 (24.4)	158.8 (25.1)	.91
Low-density cholesterol, mg/dL	0-175	84.5 (24.2)	84.5 (26.5)	.99
High-density cholesterol, mg/dL	19-110	55.8 (14.4)	54.3 (12.5)	.24
Triglycerides, mg/dL	28-240	101.8 (48.2)	115.9 (69.7)	.13
Blood urea nitrogen, mg/dL	5-25	12.4 (3.2)	11.3 (3.2)	.02
Creatinine, mg/dL	0.2-1.4	0.57 (0.12)	0.60 (0.11)	.03
Estimated glomerular filtration rate, mL/min		118.4 (41.0)	113.9 (36.2)	.17
Calcium, mg/dL	8-11	9.5 (0.5)	9.7 (0.4)	<.001
Phosphorus, mg/dL	2.7-6.5	4.7 (0.7)	4.6 (0.8)	.54
Thyrotropin, mIU/L	0.35-7.00	2.1 (1.3)	5.2 (2.8)	<.001
Total triiodothyronine, ng/dL	45-225	165.8 (34.6)	156.3 (29.1)	.03
Free thyroxine, ng/dL	0.65-3.00	1.13 (0.19)	1.05 (0.20)	.013
Prolactin, ng/mL	0-27	7.6 (5.1)	7.5 (6.8)	.88
Glucose, mg/dL	60-199	87.0 (14.9)	83.6 (13.8)	.12
Specific gravity	1.001-1.045	1.021 (0.007)	1.013[k] (0.006)	<.001
White blood cell count, $\times 10^3/\mu L$	3.0-15.5	6.9 (1.9)	No/S	
Platelet count, $\times 10^3/\mu L$	130-475	297.7 (54.5)	No/S	
Alanine aminotransferase, U/L	0-65	25.8 (10.5)	No/S	
Aspartate aminotransferase, U/L	2-65	28.9 (8.1)	No/S	
Protein, g/dL	5.5-9.0	7.42 (0.53)	No/S	
Albumin, g/dL	0.8-5.6	4.4 (0.4)	No/S	
Alkaline phosphatase, U/L	60-550	230.9 (71.3)	No/S	
Total bilirubin, mg/dL	0.1-1.3	0.38 (0.21)	No/S	
Conjugated bilirubin, mg/dL	0.0-0.4	0.10 (0.10)	No/S	
λ-Glutamyltransferase, U/L	2-55	17.15 (11.91)	No/S	
Electrocardiogram, ms				
PR	50-190	127.3 (18.2)	140.7[l] (20.9)	<.001
QRS	50-116	82.2 (8.3)	84.8[m] (9.0)	.015
QTc	300-440[j]	404.3 (26.6)	414.2 (29.1)	<.001

(Continued)

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Table 3. Laboratory Values at Baseline and Week 8 (continued)

Laboratory Measure[a]	Normal Range	Laboratory Value, Mean (SD): 76 Subjects Treated With Divalproex Sodium Who Completed 8 wk: Baseline	Week 8	*P* Value
Height, cm		138.3 (15.6)	139.9 (15.9)	<.001
Weight, kg		38.5 (14.9)	40.2 (16.1)	<.001
BMI		19.4 (3.8)	19.7 (4.1)	<.001
BMI percentile		71.3 (25.7)	69.5 (28.7)	.32
Total cholesterol, mg/dL	70-280	165.4 (29.6)	159.6 (30.4)	.017
Low-density cholesterol, mg/dL	0-175	92.3 (28.9)	85.6 (31.8)	.008
High-density cholesterol, mg/dL	19-110	50.4 (11.9)	54.5 (13.7)	<.001
Triglycerides, mg/dL	28-240	134.0 (72.1)	111.5 (80.3)	.015
Blood urea nitrogen, mg/dL	5-25	11.9 (3.0)	No/S	
Creatinine, mg/dL	0.2-1.4	0.54 (0.12)	No/S	
Estimated glomerular filtration rate, mL/min		118.2 (40.5)	No/S	
Calcium, mg/dL	8-11	9.5 (0.4)	No/S	
Phosphorus, mg/dL	2.7-6.5	4.7 (0.5)	No/S	
Thyrotropin, mIU/L	0.35-7.00	2.3 (1.1)	No/S	
Total triiodothyronine, ng/dL	45-225	171.1 (40.9)	No/S	
Free thyroxine, ng/dL	0.65-3.00	1.24 (0.22)	No/S	
Prolactin, ng/mL	0-27	7.0 (4.3)	7.1 (5.2)	.86
Glucose, mg/dL	60-199	90.3 (13.5)	88.8 (17.5)	.46
Specific gravity	1.001-1.045	1.021 (0.008)	1.023 (0.007)	.04
White blood cell count, $\times 10^3/\mu L$	3.0-15.5	7.0 (1.8)	6.4 (2.0)	.008
Platelet count, $\times 10^3/\mu L$	130-475	297.8 (65.9)	225.8 (55.9)	<.001
Alanine aminotransferase, U/L	0-65	23.5 (11.8)	22.7 (20.2)	.70
Aspartate aminotransferase, U/L	2-65	26.7 (6.8)	30.8 (23.5)	.11
Protein, g/dL	5.5-9.0	7.40 (0.40)	7.01 (0.56)	<.001
Albumin, g/dL	0.8-5.6	4.5 (0.3)	4.0 (0.4)	<.001
Alkaline phosphatase, U/L	60-550	244.1 (82.6)	237.9 (79.1)	.17
Total bilirubin, mg/dL	0.1-1.3	0.39 (0.23)	0.32 (0.16)	<.001
Conjugated bilirubin, mg/dL	0.0-0.4	0.08 (0.06)	0.08 (0.07)	.82
λ-Glutamyltransferase, U/L	2-55	16.5 (5.9)	16.9 (6.0)	.46
Electrocardiogram, ms				
PR	50-190	128.7 (15.0)	128.3 (14.5)	.66
QRS	50-116	82.3 (8.4)	80.4 (8.7)	.007
QTc	300-440[j]	406.6 (23.4)	401.9[n] (23.0)	.13

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); No/S, no subjects with these values (the protocol did not include running these tests for subjects); QTc, QT interval corrected for heart rate. Bonferroni-corrected *P*=.017.

SI conversion factors: To convert height to meters, multiply by 0.01; to convert total, low-, and high-density cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert blood urea nitrogen to millimoles per liter, multiply by 0.357; to convert creatinine to micromoles per liter, multiply by 88.4; to convert calcium to millimoles per liter, multiply by 0.25; to convert phosphorus to millimoles per liter, multiply by 0.323; to convert total triiodothyronine to nanomoles per liter, multiply by 0.0154; to convert free thyroxine to picomoles per liter, multiply by 12.871; to convert prolactin to picomoles per liter, multiply by 43.478; to convert glucose to millimoles per liter, multiply by 0.0555; to convert white blood cell count to $\times 10^9/L$, multiply by 0.001; to convert platelet count to $\times 10^9/L$, multiply by 1.0; to convert alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and λ-glutamyltransferase to microkatals per liter, multiply by 0.0167; to convert protein and albumin to grams per liter, multiply by 10; to convert total and conjugated bilirubin to micromoles per liter, multiply by 17.104

[a] For the following measures, at least 1 subject had a missing value for baseline and/or week 8; therefore, mean values are presented only for subjects with both data points available: total cholesterol (61 subjects treated with lithium and 75 subjects treated with divalproex sodium), low-density cholesterol (73 subjects treated with divalproex sodium), total triiodothyronine (56 subjects treated with lithium), free thyroxine (57 subjects treated with lithium), specific gravity (77 subjects treated with risperidone), protein (74 subjects treated with divalproex sodium), albumin (75 subjects treated with divalproex sodium), and conjugated bilirubin (74 subjects treated with divalproex sodium).

[b] Significant difference between increased weight and BMI with risperidone and increased weight and BMI with lithium (*P*<.001) and increased weight and BMI with divalproex sodium (*P*<.001).

[c] Significant difference between increased low-density cholesterol with risperidone and decreased low-density cholesterol with divalproex sodium (*P*=.005).

[d] Significant difference between decreased high-density cholesterol with risperidone and increased high-density cholesterol with divalproex sodium (*P*=.008).

[e] Significant difference between increased prolactin with risperidone and decreased prolactin with lithium (*P*<.001) and increased prolactin with divalproex sodium (*P*<.001).

[f] Significant difference between increased glucose with risperidone and decreased glucose with lithium (*P*=.003).

[g] Significant difference between decreased specific gravity with risperidone and increased specific gravity with divalproex sodium (*P*<.001).

[h] Significant difference between decreased protein with risperidone and decreased protein with divalproex sodium (*P*<.001).

[i] Significant difference between decreased albumin with risperidone and decreased albumin with divalproex sodium (*P*<.001)

[j] Twenty subjects had at least 1 QTc measurement that was greater than 440 milliseconds (9.0% of subjects treated with risperidone were in the range of 445-493 milliseconds; 10.0% of subjects treated with lithium were in the range of 443-472 milliseconds; and 3.0% of subjects treated with divalproex sodium were in the range of 442-449 milliseconds).

[k] Significant difference between decreased specific gravity with lithium and decreased specific gravity with risperidone (*P*<.001) and increased specific gravity with divalproex sodium (*P*<.001)

[l] Significant difference between increased PR with lithium and decreased PR with risperidone (*P*<.001) and decreased PR with divalproex sodium (*P*<.001).

[m] Significant difference between increased QRS with lithium and decreased QRS with divalproex sodium (*P*<.001).

[n] Significant difference between decreased QTc with divalproex sodium and increased QTc with risperidone (*P*=.017) and increased QTc with lithium (*P*<.001).

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Table 4. Adverse Effects and Modified AIMS Scores at Baseline and at Least 1 Week During Weeks 1 to 8

Adverse Effect[a]	Subjects,[b] No. (%) Treated With Risperidone and Completed ≥1 wk (n=89) Baseline	Weeks 1-8	P Value
Weight loss	1 (1.1)	9 (10.1)[c]	.011
Appetite increase	23 (25.8)	68 (76.4)	<.001
Weight gain	11 (12.4)	85 (95.5)[d]	<.001
Constipation	2 (2.2)	7 (7.9)	.06
Nausea	0 (0.0)	15 (16.9)[e]	
Vomiting	0 (0.0)	7 (7.9)[f]	
Headache	10 (11.2)	28 (31.5)	<.001
Difficulty falling asleep	71 (79.8)	33 (37.1)[g]	<.001
Drowsiness	16 (18.0)	45 (50.6)[h]	<.001
Sweating	1 (1.1)	6 (6.7)	.03
Dry mouth	1 (1.1)	9 (10.1)	.011
Nasal congestion	5 (5.6)	20 (22.5)	<.001
Frequent urination	2 (2.2)	6 (6.7)[i]	.16
Itching	3 (3.4)	6 (6.7)	.26
Rash	3 (3.4)	6 (6.7)	.32
Excessive thirst	3 (3.4)	22 (24.7)	<.001
Fever	0 (0.0)	9 (10.1)	
Modified AIMS score			
≥2	3 (3.4)	8 (9.0)	.06
≥3	2 (2.2)	6 (6.7)	.05
	Treated With Lithium and Completed ≥1 wk (n=84)		
	Baseline	**Weeks 1-8**	
Abdominal pain	5 (6.0)	34 (40.5)	<.001
Appetite decrease	12 (14.3)	24 (28.6)	.011
Weight loss	4 (4.8)	23 (27.4)	<.001
Weight gain	7 (8.3)	58 (69.0)	<.001
Diarrhea	1 (1.2)	9 (10.7)	.011
Nausea	0 (0.0)	30 (35.7)	
Vomiting	0 (0.0)	18 (21.4)	
Headache	8 (9.5)	29 (34.5)	<.001
Drowsiness	10 (11.9)	22 (26.2)	.019
Sweating	1 (1.2)	7 (8.3)	.03
Tremor	0 (0.0)	7 (8.3)	
Lethargy	12 (14.3)	25 (29.8)	.012
Dry mouth	1 (1.2)	18 (21.4)[j]	<.001
Nasal congestion	3 (3.6)	20 (23.8)	<.001
Frequent urination	2 (2.4)	24 (28.6)	<.001
Enuresis	6 (7.1)	18 (21.4)	.001
Rash	2 (2.4)	5 (6.0)	.26
Muscular cramps	1 (1.2)	5 (6.0)	.05
Excessive thirst	3 (3.6)	37 (44.0)[k]	<.001
Fever	2 (2.4)	5 (6.0)	.18
Modified AIMS score of ≥1	3 (3.6)	5 (6.0)	.41

(Continued)

Table 4. Adverse Effects and Modified AIMS Scores at Baseline and at Least 1 Week During Weeks 1 to 8 (continued)

Adverse Effect[a]	Subjects,[b] No. (%) Treated With Divalproex Sodium and Completed ≥1 wk (n=97) Baseline	Weeks 1-8	P Value
Abdominal pain	11 (11.3)	26 (26.8)	.005
Appetite decrease	10 (10.3)	21 (21.6)	.016
Weight loss	4 (4.1)	29 (29.9)	<.001
Appetite increase	28 (28.9)	69 (71.1)	<.001
Weight gain	7 (7.2)	71 (73.2)	<.001
Diarrhea	2 (2.1)	17 (17.5)	<.001
Nausea	1 (1.0)	23 (23.7)	<.001
Vomiting	0 (0.0)	11 (11.3)	
Difficulty arousing in AM	28 (28.9)	62 (63.9)[l]	<.001
Drowsiness	11 (11.3)	34 (35.1)	<.001
Nasal congestion	7 (7.2)	28 (28.9)	<.001
Frequent urination	4 (4.1)	14 (14.4)	.012
Enuresis	10 (10.3)	20 (20.6)	.008
Itching	5 (5.2)	16 (16.5)	.008
Rash	3 (3.1)	13 (13.4)	.004
Excessive thirst	4 (4.1)	19 (19.6)	.002
Fever	1 (1.0)	9 (9.3)	.011

Abbreviation: AIMS, Abnormal Involuntary Movement Scale.

[a] Adverse effects were considered present if the severity score was a 2 or 3 on a scale of 0 to 3. The only adverse effects presented are those that occurred in at least 5% of subjects who were treated with the given medication and that had at least a 2-fold increase or decrease during the study (Bonferroni-corrected $P=.017$).

[b] Of the 89 subjects treated with risperidone, 90 subjects treated with lithium, and 100 subjects treated with divalproex sodium who completed the baseline assessment, 89, 84, and 97 had at least 1 weekly rating, respectively.

[c] Significantly less weight loss with risperidone than with lithium ($P=.005$) or divalproex sodium ($P=.001$).

[d] Significantly more weight gain with risperidone than with lithium ($P<.001$) or divalproex sodium ($P<.001$).

[e] Significantly less nausea with risperidone than with lithium ($P=.006$).

[f] Significantly less vomiting with risperidone than with lithium ($P=.015$).

[g] Significantly less difficulty falling asleep with risperidone than with lithium ($P<.001$) or divalproex sodium ($P<.001$).

[h] Significantly more drowsiness with risperidone than with lithium ($P=.001$).

[i] Significantly less abdominal pain and less frequent urination with risperidone than with lithium ($P<.001$).

[j] Significantly more dry mouth with lithium than with divalproex sodium ($P=.008$).

[k] Significantly more excessive thirst with lithium than with risperidone ($P=.008$) or divalproex sodium ($P<.001$).

[l] Significantly more difficulty arousing in AM with divalproex sodium than with risperidone ($P<.001$) or lithium ($P<.001$).

COMMENT

Risperidone was significantly superior to lithium and divalproex sodium on the primary outcome measure (CGI-BP-IM) for acute treatment of pediatric mania. In addition, greater tolerability for risperidone compared with lithium was evidenced by significantly higher discontinuation rates in the lithium group. Compliance by both pill count and lithium levels was excellent (coefficient of variation, 0.18). Finding that risperidone was the most efficacious medication compared with lithium and divalproex sodium is consistent with studies that found second-generation antipsychotic drugs for childhood mania to be more efficacious than placebo and with studies that had negative findings for divalproex sodium.[10-15] A recent study[9] showed a similar outcome for risperidone vs divalproex sodium, but with a much higher response rate. That sample, however, had only 22% subjects with psychosis compared with 77.1% in the TEAM study.

Response rates at relatively low doses of risperidone suggest that clinicians can be more conservative with this

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medication. The difference in severity on CGI-BP-SM by recruitment from media advertisements or from other sources was likely not clinically meaningful because scores of both 5.89 and 6.23 signify marked severity.

Differences in outcome by site occur across studies (see, eg, the NIMH-funded TORDIA [Treatment of SSRI-Resistant Depression in Adolescents] project).[33] In the TEAM study, however, all outcomes, whether significant or nonsignificant, were in the same direction across sites. Future mediator and moderator publications will examine site differences.

Although the response rate was significantly higher in the risperidone group, weight gain, BMI increase, and presence of hyperprolactinemia were significantly worse. These metabolic factors and electrocardiographic changes observed in the lithium and divalproex sodium groups require monitoring. The decreased lipid levels in the divalproex sodium group are consistent with the salutatory effects of valproate preparations on lipid levels in epileptic children.[34] The significantly increased thyrotropin levels in subjects treated with lithium, although not to out-of-range levels, argues for monitoring thyrotropin levels early in treatment. It is unclear why the Modified AIMS scores for the subjects treated with risperidone were low, considering that dystonia and akathisia may emerge early in neuroleptic treatment.[35]

Overall, compared with registration studies, the TEAM study had higher rates of adverse events. Without a placebo group, it is not possible to ascertain whether these are true increases. But speculations on the higher rate include that the assessment methods for adverse events were more rigorous in the TEAM study than in usual registration studies. In the TEAM study, each possible adverse effect was queried individually by highly experienced research clinicians from both primary caretakers and subjects. These detailed methods differ from open-ended, usually single-informant assessments in registration studies. Differences in prevalence of adverse events between open-ended questions and interviews that inquire about specific adverse occurrences have been shown.[36]

The limitations of the TEAM study include that, at this point in time, there is no valid diagnostic biological measure for childhood bipolar disorders, and thus no schema for clinical assessment has been biologically validated. Therefore, the best that investigators can do is to use methods that can be independently replicated. The methods used in the TEAM study, we believe, accomplished this goal by using rigorous consensus diagnoses and comprehensive, reliable methods. But the TEAM findings may not generalize to studies that use other methods. The age of onset was very young using the comprehensive study assessments, but validity of preschool diagnoses will have to await further research. Blood samples were obtained from nonfasting subjects, but recent work has shown that nonfasting triglycerides are better predictors of stroke risk[37] and of cardiovascular risk.[38] Stable, preprotocol psychosocial interventions, preprotocol, stable stimulants, and tapered antidepressants were not standardized, but none of these affected outcome measures. There were too few nonpsychotic subjects for meaningful analyses of this subgroup.

In conclusion, risperidone is significantly more efficacious than lithium or divalproex sodium in the initial management of mania in children, but it is associated with adverse effects such as weight gain and hyperprolactinemia that raise concern for long-term treatment. Pursuing a safer and more efficacious intervention for childhood mania remains a research priority.

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coordinating site did not participate in data collection and, therefore, did not receive study medication from Abbott. The second site at Washington University in St Louis was a data collection site (PI: Dr Luby).

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