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

Barbara Geller, MD; Joan L. Luby, MD; Paramjit Joshi, MD; Karen Dineen Wagner, MD, PhD; Graham Emslie, MD; John T. Walkup, MD; David A. Axelson, MD; Kristine Bolhofner, BS; Adelaide Robb, MD; Dwight V. Wolf, MD; Mark A. Riddle, MD; Boris Birmaher, MD; Nasima Nusrat, MD; Neal D. Ryan, MD; Benedetto Vitiello, MD; Rebecca Tillman, MS; Philip Lavori, PhD

**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 (χ^2=16.9, *P* <.001) and vs divalproex sodium (χ^2=28.3, *P* <.001). Response to lithium vs divalproex sodium did not differ. The discontinuation rate was higher for lithium than for risperidone (χ^2=6.4, *P* =.011). Increased weight gain, body mass index, and prolactin level occurred with risperidone vs lithium (F=45.5, *P* <.001; F=39.1, *P* <.001; and F=191.4, *P* <.001, respectively) and vs divalproex sodium (F=34.7, *P* <.001; F=45.3, *P* <.001; and F=209.4, *P* <.001, respectively). The thyrotropin level increased in subjects taking lithium (t=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

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) score of 60 or less at baseline and in good physical health. Co-occurring attention-deficit hyperactivity, oppositional defiant, and conduct disorders were allowed because these are common comorbidities in childhood mania. 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. 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.

STUDY INTERVENTION

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. Effects of mixed mania, psychosis, and rapid cycling were used because of the differential response in some studies of adults. 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 random 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
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.\textsuperscript{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.\textsuperscript{25} Geller et al\textsuperscript{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...
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 provides 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 inter-rater reliability of 90% for mania symptoms and psychiatric diagnoses on the WASH-U-KSADS.29

**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 non-fasting.

**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, these subjects could appear for the week-2 assessment. 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-

<table>
<thead>
<tr>
<th>Table 1. Titration Schedule for the TEAM Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight at Visit</strong></td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Dispensing visit</td>
</tr>
<tr>
<td>0.25 mg twice a day</td>
</tr>
<tr>
<td>25-50 kg</td>
</tr>
<tr>
<td>0.5 mg twice a day</td>
</tr>
<tr>
<td>50 kg</td>
</tr>
<tr>
<td>0.5 mg twice a day</td>
</tr>
<tr>
<td>All weights at week 1</td>
</tr>
<tr>
<td>All weights at week 2</td>
</tr>
<tr>
<td>&lt;25 kg</td>
</tr>
<tr>
<td>25-50 kg</td>
</tr>
<tr>
<td>&gt;50 kg</td>
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<tr>
<td>All weights at week 3</td>
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<tr>
<td>All weights at week 4</td>
</tr>
<tr>
<td>&lt;25 kg</td>
</tr>
<tr>
<td>25-50 kg</td>
</tr>
<tr>
<td>&gt;50 kg</td>
</tr>
<tr>
<td>All weights at week 5</td>
</tr>
<tr>
<td>All weights at week 6</td>
</tr>
<tr>
<td>&lt;25 kg</td>
</tr>
<tr>
<td>25-50 kg</td>
</tr>
<tr>
<td>&gt;50 kg</td>
</tr>
<tr>
<td>All weights at week 7</td>
</tr>
<tr>
<td>All weights at week 8</td>
</tr>
</tbody>
</table>

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.
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 ($\chi^2=1.4, P = .30$). 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 (cTable 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%; $\chi^2=6.4, P = .011$). The discontinuation rates did not differ between the risperidone and divalproex sodium groups (15.7% vs 26.0%; $\chi^2=2.9, P = .09$) or between the lithium and divalproex sodium groups (32.2% vs 26.0%; $\chi^2=0.9, P = .35$).

**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.

**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 (93.8% for risperidone, 94.7% for lithium, and 97.1% for divalproex sodium).
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]; \(\chi^2=16.9, P<.001\)) and those treated with divalproex sodium (68.5% [n=61] vs 24.0% [n=24]; \(\chi^2=28.3, P<.001\)). 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% [\(\chi^2=8.5, P=.004\)] or 48.3% vs 17.0% [\(\chi^2=16.5, P<.001\)], respectively) and absence of mania diagnosis (62.9% vs 41.1% [\(\chi^2=6.1, P=.013\)] or 62.9% vs 26.0% [\(\chi^2=19.1, P<.001\)], respectively).

Separate analyses of the primary outcome were conducted for 218 subjects aged 6 to 12 years and 61 sub-
Table 2. Baseline Demography, Mania Characteristics, and Comorbid Diagnoses of Children and Adolescents in the TEAM Studya (continued)

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

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 = .02) 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.

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.
received lithium (2.1 [1.3] vs 5.2 [2.8] mIU/L; $P < .001$). 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 female subject who was hospitalized after running into the street, despite oncoming traffic, after accusing her 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 1.8% 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]; $\chi^2 = 0.1, P = .77$), for subjects continuing stable, preprotocol psychosocial interventions vs subjects not receiving psychosocial interventions (47.8% [11 of 23] vs 41.4% [106 of 256]; $\chi^2 = 0.0, P = .99$), or for subjects continuing stable, preprotocol stimulant tapering during week 1 (10.1% of the risperidone group, 8.9% of the lithium group, and 10.0% of the divalproex sodium group used stimulant medications), in antidepres-

### 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) increase in low-density cholesterol level in the risperidone group and the mean (SD) decrease in 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) decrease in high-density cholesterol level in the risperidone group and the mean (SD) increase in high-density cholesterol level in the divalproex sodium group (–2.3 [18.4] vs +3.8 [6.6] mg/dL; to convert to millimoles per liter, multiply by 0.0259; $F_{1,213} = 7.3, P = .008$). The mean (SD) thymotropin level significantly increased between baseline and week 8 in subjects who received lithium (2.1 [1.3] vs 3.2 [2.8] mIU/L; $t_{65} = 11.3, P < .001$).
Table 3. Laboratory Values at Baseline and Week 8

<table>
<thead>
<tr>
<th>Laboratory Measure</th>
<th>Normal Range</th>
<th>Baseline</th>
<th>Week 8</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Height, cm</strong></td>
<td></td>
<td>142.5 (17.5)</td>
<td>143.4 (17.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td></td>
<td>40.7 (18.4)</td>
<td>44.0 (19.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td>19.1 (4.5)</td>
<td>20.4 (4.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>BMI percentile</strong></td>
<td></td>
<td>59.8 (26.1)</td>
<td>74.4 (16.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Total cholesterol, mg/dL</strong></td>
<td>70-280</td>
<td>163.1 (35.4)</td>
<td>151.7 (31.9)</td>
<td>.51</td>
</tr>
<tr>
<td><strong>Low-density cholesterol, mg/dL</strong></td>
<td>0-175</td>
<td>81.5 (32.7)</td>
<td>191.4 (29.1)</td>
<td>.25</td>
</tr>
<tr>
<td><strong>High-density cholesterol, mg/dL</strong></td>
<td>19.1-110</td>
<td>54.0 (19.8)</td>
<td>51.7 (12.2)</td>
<td>.28</td>
</tr>
<tr>
<td><strong>Triglycerides, mg/dL</strong></td>
<td>28-240</td>
<td>113.7 (69.5)</td>
<td>115.9 (72.2)</td>
<td>.78</td>
</tr>
<tr>
<td><strong>Blood urea nitrogen, mg/dL</strong></td>
<td>5-25</td>
<td>16.1 (2.8)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Creatinine, mg/dL</strong></td>
<td>0.2-1.4</td>
<td>0.61 (0.14)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Estimated glomerular filtration rate, mL/min</strong></td>
<td>112.7 (50.8)</td>
<td>112.7 (50.8)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium, mg/dL</strong></td>
<td>8-11</td>
<td>9.5 (0.5)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Phosphorus, mg/dL</strong></td>
<td>2.7-6.5</td>
<td>4.6 (0.6)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Thyrotropin, mIU/L</strong></td>
<td>0.35-7.0</td>
<td>1.9 (0.9)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Total triiodothyronine, ng/dL</strong></td>
<td>45-225</td>
<td>161.6 (35.9)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Free thyroxine, ng/dL</strong></td>
<td>0.65-3.0</td>
<td>1.17 (0.29)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Prolactin, ng/mL</strong></td>
<td>0-27</td>
<td>4.8 (0.8)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Glucose, mg/dL</strong></td>
<td>60-200</td>
<td>48.9 (14.3)</td>
<td>91.3 (15.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Specific gravity</strong></td>
<td>1.001-1.045</td>
<td>1.020 (0.007)</td>
<td>1.019 (0.007)</td>
<td>.37</td>
</tr>
<tr>
<td><strong>White blood cell count, ×10^3/µL</strong></td>
<td>3.0-15.5</td>
<td>6.4 (1.5)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Platelet count, ×10^3/µL</strong></td>
<td>130-475</td>
<td>289.4 (68.8)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Alanineaminotransferase, U/L</strong></td>
<td>0-65</td>
<td>25.7 (17.5)</td>
<td>30.4 (24.1)</td>
<td>.014</td>
</tr>
<tr>
<td><strong>Aspartateaminotransferase, U/L</strong></td>
<td>2-6.5</td>
<td>26.8 (8.1)</td>
<td>28.3 (12.1)</td>
<td>.14</td>
</tr>
<tr>
<td><strong>Protein, g/dL</strong></td>
<td>5.5-9.0</td>
<td>7.35 (0.4)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Total bilirubin, mg/dL</strong></td>
<td>0.1-1.3</td>
<td>0.46 (0.33)</td>
<td>0.40 (0.29)</td>
<td>.018</td>
</tr>
<tr>
<td><strong>Conjugated bilirubin, mg/dL</strong></td>
<td>0.0-0.4</td>
<td>0.10 (0.08)</td>
<td>0.10 (0.07)</td>
<td>.77</td>
</tr>
<tr>
<td><strong>γ-Glutamyltransferase, U/L</strong></td>
<td>2-55</td>
<td>18.3 (9.7)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td><strong>Electrocardiogram, ms</strong></td>
<td>PR</td>
<td>130.0 (16.9)</td>
<td>128.4 (16.7)</td>
<td>.22</td>
</tr>
<tr>
<td><strong>QRS</strong></td>
<td>50-116</td>
<td>82.9 (7.2)</td>
<td>82.9 (7.4)</td>
<td>.92</td>
</tr>
<tr>
<td><strong>QTc</strong></td>
<td>300-440</td>
<td>406.9 (22.0)</td>
<td>410.2 (27.8)</td>
<td>.09</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Measure</th>
<th>Normal Range</th>
<th>Baseline</th>
<th>Week 8</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, cm</td>
<td>138.3 (15.6)</td>
<td>139.9 (15.9)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>38.5 (14.9)</td>
<td>40.2 (16.1)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>19.4 (3.8)</td>
<td>19.7 (4.1)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>BMI percentile</td>
<td>71.3 (25.7)</td>
<td>69.5 (26.7)</td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>70-280</td>
<td>165.4 (29.6)</td>
<td>159.6 (30.4)</td>
<td>.017</td>
</tr>
<tr>
<td>Low-density cholesterol, mg/dL</td>
<td>0-175</td>
<td>92.3 (28.9)</td>
<td>85.6 (31.8)</td>
<td>.008</td>
</tr>
<tr>
<td>High-density cholesterol, mg/dL</td>
<td>19-110</td>
<td>50.4 (11.9)</td>
<td>54.5 (13.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>28-240</td>
<td>134.0 (72.1)</td>
<td>111.5 (80.3)</td>
<td>.015</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>5-25</td>
<td>11.9 (3.0)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.2-1.4</td>
<td>0.54 (0.12)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min</td>
<td>118.2 (40.5)</td>
<td>No/S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>8-11</td>
<td>9.5 (0.4)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td>Phosphorus, mg/dL</td>
<td>2.7-6.5</td>
<td>4.7 (0.5)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td>Thyrotopin, mIU/L</td>
<td>0.35-7.0</td>
<td>2.3 (1.1)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td>Total triiodothyronine, ng/dL</td>
<td>45-225</td>
<td>171.1 (40.9)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td>Free thyroxine, ng/dL</td>
<td>0.65-5.0</td>
<td>1.24 (0.22)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td>Prolactin, ng/mL</td>
<td>0.2-27</td>
<td>7.0 (4.3)</td>
<td>.88</td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>60-199</td>
<td>90.3 (13.5)</td>
<td>.46</td>
<td></td>
</tr>
<tr>
<td>Protein, g/dL</td>
<td>5.5-9.0</td>
<td>7.1 (5.2)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.0-15.5</td>
<td>6.4 (2.0)</td>
<td>.008</td>
<td></td>
</tr>
<tr>
<td>Platelet count, ×10^12/L</td>
<td>130-475</td>
<td>297.8 (65.9)</td>
<td>225.8 (55.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alkaline aminotransferase, U/L</td>
<td>0-65</td>
<td>23.5 (11.8)</td>
<td>22.7 (20.2)</td>
<td>.70</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>2-65</td>
<td>26.7 (6.8)</td>
<td>30.8 (23.5)</td>
<td>.11</td>
</tr>
<tr>
<td>Protein, g/dL</td>
<td>5.5-9.0</td>
<td>7.0 (4.3)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>4.5 (0.3)</td>
<td>4.0 (0.4)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>0-5-5.6</td>
<td>1.24 (0.22)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>0.1-1.3</td>
<td>0.39 (0.23)</td>
<td>0.32 (0.16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Conjugated bilirubin, mg/dL</td>
<td>0.0-0.4</td>
<td>0.08 (0.06)</td>
<td>0.08 (0.07)</td>
<td>.82</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>134.0 (72.1)</td>
<td>111.5 (80.3)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>72.8 (13.6)</td>
<td>72.8 (13.6)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>112.5 (20.2)</td>
<td>112.5 (20.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>60-199</td>
<td>90.3 (13.5)</td>
<td>.46</td>
<td></td>
</tr>
<tr>
<td>Protein, g/dL</td>
<td>5.5-9.0</td>
<td>7.1 (5.2)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>171.1 (40.9)</td>
<td>No/S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram, ms</td>
<td>50-190</td>
<td>128.7 (15.0)</td>
<td>128.3 (14.5)</td>
<td>.66</td>
</tr>
<tr>
<td>PR</td>
<td>50-190</td>
<td>82.3 (8.4)</td>
<td>No/S</td>
<td></td>
</tr>
<tr>
<td>QRS</td>
<td>50-116</td>
<td>80.4 (8.7)</td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td>QTc</td>
<td>50-116</td>
<td>80.4 (8.7)</td>
<td>.007</td>
<td></td>
</tr>
</tbody>
</table>

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 0.026; 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 potassium to millimoles per liter, multiply by 0.357; to convert glucose to millimoles per liter, multiply by 0.0555; to convert white blood cell count to /µL, multiply by 1.0; to convert alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and γ-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.

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).

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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. A recent study 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

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

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Treated With Risperidone and Completed ≥1 wk (n=89)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>1 (1.1)</td>
<td>9 (10.1)</td>
</tr>
<tr>
<td>Appetite</td>
<td>23 (25.8)</td>
<td>68 (76.4)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>11 (12.4)</td>
<td>85 (95.5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (2.2)</td>
<td>7 (7.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0)</td>
<td>15 (16.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0.0)</td>
<td>7 (7.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (11.2)</td>
<td>28 (31.5)</td>
</tr>
<tr>
<td>Difficulty falling asleep</td>
<td>71 (79.8)</td>
<td>33 (37.1)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>16 (18.0)</td>
<td>45 (50.6)</td>
</tr>
<tr>
<td>Sweating</td>
<td>1 (1.1)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (1.1)</td>
<td>9 (10.1)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>5 (5.6)</td>
<td>20 (22.6)</td>
</tr>
<tr>
<td>Frequent urination</td>
<td>2 (2.2)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Itching</td>
<td>3 (3.4)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (3.4)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Excessive thirst</td>
<td>3 (3.4)</td>
<td>22 (24.7)</td>
</tr>
<tr>
<td>Fever</td>
<td>0 (0.0)</td>
<td>9 (10.1)</td>
</tr>
<tr>
<td>Modified AIMS score</td>
<td>≥2</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>2 (2.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Treated With Lithium and Completed ≥1 wk (n=84)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>5 (6.0)</td>
<td>34 (40.5)</td>
</tr>
<tr>
<td>Appetite decrease</td>
<td>12 (14.3)</td>
<td>24 (28.6)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>4 (4.8)</td>
<td>23 (27.4)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>7 (8.3)</td>
<td>58 (69.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1.2)</td>
<td>9 (10.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0)</td>
<td>30 (35.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0.0)</td>
<td>18 (21.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (9.5)</td>
<td>29 (34.5)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>10 (11.9)</td>
<td>22 (26.2)</td>
</tr>
<tr>
<td>Sweating</td>
<td>1 (1.2)</td>
<td>7 (8.3)</td>
</tr>
<tr>
<td>Tremor</td>
<td>0 (0.0)</td>
<td>7 (8.3)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>12 (14.3)</td>
<td>25 (29.8)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (1.2)</td>
<td>18 (21.4)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>3 (3.6)</td>
<td>20 (23.8)</td>
</tr>
<tr>
<td>Frequent urination</td>
<td>2 (2.4)</td>
<td>24 (28.6)</td>
</tr>
<tr>
<td>Enuresis</td>
<td>6 (7.1)</td>
<td>18 (21.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (2.4)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>Muscular cramps</td>
<td>1 (1.2)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>Excessive thirst</td>
<td>3 (3.6)</td>
<td>37 (44.0)</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (2.4)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>Modified AIMS score of ≥1</td>
<td>3 (3.6)</td>
<td>5 (6.0)</td>
</tr>
</tbody>
</table>

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 difficulty arousing in AM with divalproex sodium than with risperidone.
k Significantly more dry mouth with lithium than with divalproex sodium (P=.008).
l Significantly more excessive thirst with lithium than with risperidone (P=.008) or divalproex sodium (P<.001).
m Significantly more difficulty arousing in AM with divalproex sodium than with risperidone (P<.001) or lithium (P=.001).
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). 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 salutary effects of valproate preparations on lipid levels in epileptic children. The significantly increased 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.

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.

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 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 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 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
reports the following from outside the submitted work: employment at Children’s National Medical Center in Washington, DC. Dr Wagner reports the following from the work under consideration: grant from NIMH and provision of medicines from Abbott. Dr Wagner also reports the following from outside the submitted work: consultancy for Forest, American Institute of Biological Sciences, Krog and Partners, and National Institutes of Health; employment at University of Texas Medical Branch in Galveston; payment for lectures from American Psychiatric Association, Letters and Sciences, American Society of Clinical Psychopharmacology, Toledo Hospital, American Academy of Child and Adolescent Psychiatry, Madison Institute of Medicine, Mexican Psychiatric Association, Contemporary Forums, Doctors Hospital at Renaissance, CME LLC, Nevada Psychiatric Association, and Quantia Communications; payment for manuscript preparation from Guilford Publications, Health and Wellness Education Partners, American Psychiatric Publishing Inc, Springer Publishing, CMP Medica, UBM Medica, and Wolters Kluwer Health; payment from Physician’s Postgraduate Press, Inc, for serving as deputy editor of the Journal of Clinical Psychiatry. Dr Wagner also sits on the Scientific Advisory Board of the Child and Adolescent Bipolar Foundation and on the Scientific Advisory Board of the Depression and Bipolar Support Alliance. Dr Emulsie reports the following from the work under consideration: a grant from NIMH and provision of medicines from Abbott. Dr Emulsie also reports the following from outside the submitted work: consultancy for Biobehavioral Diagnostics, Inc, Eli Lilly, Forest, GlaxoSmithKline, Pfizer, Shire, Validus, and Wyeth; employment at University of Texas Southwestern Medical Center; grants/grants pending from NIMH, Biobehavioral Diagnostics, Inc, Eli Lilly, Forest, GlaxoSmithKline, Shire, and Somerset; payment for lectures, including service on speakers bureaus from Forest; and receiving payment for manuscript preparation from British Medical Journal Online. Dr Walkup reports the following for the work under consideration: a grant from NIMH; support for travel to meetings from NIMH; and provision of medicines from Abbott. Dr Axelson reports the following for the work under consideration: a grant from NIMH. Ms Bolhofner reports the following for the work under consideration: a grant from NIMH. Ms Bolhofner also reports the following from outside the submitted work: employment at Washington University in St Louis, Missouri, and grants from NIMH. Dr Robb reports the following for the work under consideration: a grant from NIMH; support for travel to meetings from NIMH; provision of medicines from Abbott; and payment for serving as clinical pharmacologist for the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Dr Robb also reports the following from outside the submitted work: board membership at Lilly, Bristol Myers Squibb, Otsuka, Shionogi, and McNeil Pharmaceuticals; consultancy for Lundbeck; employment at Children’s National Medical Center; expert testimony for a case on antipsychotic use; grants/grants pending from Bristol Meyers Squibb, McNeil Pediatrics, Merck Schieving Plough, GlaxoSmithKline, Janssen, Sepracor, Supernus, Otsuka, Pfizer, Johnson and Johnson, and Forest; payment for service on speakers bureaus from Bristol Myers Squibb, Lilly, and McNeil Pediatrics; royalties from Epocrates; payment for development of education presentations from University of Minnesota, American Academy of Child & Adolescent Psychiatry, and American Academy of Pediatrics; stock/stock options from Lilly, Pfizer, Johnson and Johnson, GlaxoSmithKline, and 3M. Dr Robb also sits on the Children and Adults with Attention-Deficit/Hyperactivity Disorder professional advisory board and program committee for the American Psychiatric Association annual meeting, and her husband sits on American Epilepsy Society Board and Scientific Committee for Child Neurology Society. Dr Wolf reports the following for the work under consideration: a grant from NIMH. Dr Riddle reports the following for the work under consideration: a grant from NIMH and provision of medicines from Abbott. Dr Riddle also reports the following from outside the submitted work: employment at Johns Hopkins University; expert testimony for Teva Canada; and receiving aripiprazole for an NIMH study. Dr Birmaher also reports the following for the work under consideration: a grant from NIMH. Dr Birmaher also reports the following from outside the submitted work: consultancy for Schering Plough, Dey Pharma, Forest, and Jazz Pharmaceuticals; and royalties from Random House and Lippincott Williams and Wilkins. Dr Nusrat reports the following for the work under consideration: a grant from NIMH; support for travel to meetings from NIMH; and provision of medicines from Abbott. Dr Nusrat also reports the following from outside the submitted work: employment at Children’s National Medical Center and grants/grants pending from Merck/Scherring Plough, GlaxoSmithKline, Janssen, Sepracor, Supernus, Otsuka, Pfizer, Johnson and Johnson, and Forest. Dr Ryan reports the following for the work under consideration: a grant from NIMH; support for travel to meetings from NIMH; and provision of medicines from Abbott. Dr Ryan also reports the following from outside the submitted work: employment at the University of Pittsburgh and the University of Pittsburgh Medical Center. Ms Tillman reports the following for the work under consideration: a grant from NIMH and payment for writing or reviewing the manuscript from NIMH. Ms Tillman also reports the following from outside the submitted work: employment at Washington University in St Louis and receiving travel/accommodations/meeting expenses from NIMH. Dr Lavori reports the following for the work under consideration: a grant from NIMH.

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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).

Disclaimer: The opinions and assertions contained in this report are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of Health and Human Services, the National Institutes of Health, or the NIMH.


REFERENCES


