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Double-Blind Randomized Trial of Risperidone versus Divalproex in Pediatric Bipolar Disorder

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Abstract

Objective—To determine the relative effects of risperidone and divalproex in pediatric mania.

Methods—This is a double-blind randomized outpatient clinical trial with 66 children and adolescents (mean age=10.9± 3.3 years; age range = 8 to 18 years) with mania who were randomly assigned to either risperidone (0.5–2 mg/day, $n = 33$) or divalproex (60–120 µg/ml, $n = 33$) for a 6-week period. Measures included the Young Mania Rating Scale (YMRS) and Child Depression Rating Scale- Revised (CDRS-R).

Results—Mixed-effects regression models, with interaction between time and the active drug as predictors, found that the risperidone group had more rapid improvement than the divalproex group ($p < 0.05$), although final scores did not differ significantly between groups. Mixed models using only those subjects who completed the 6-week study found similar results. The response rate on YMRS was 78.1% for risperidone and 45.5% for divalproex ($p < .01$). The remission rate for risperidone was 62.5%, compared with 33.3% for divalproex ($p < .05$). Improvement on the CDRS-R was significantly higher for the risperidone group relative to the divalproex group ($p < .05$). There were no significant differences between groups in safety, but subject retention was significantly higher at study endpoint in the risperidone group ($p < 0.01$). Drop out rate was 24% in risperidone group and 48% in divalproex group, with increased irritability being the most common reason for drop out in the latter. There was no significant weight gain in either group.

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DISCLOSURE

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Conclusion—Results suggest that risperidone was associated with more rapid improvement and greater reduction in manic symptoms compared to divalproex. Although the results suggest that both drugs are safe, risperidone's lower attrition rate and lower rate of adverse events may suggest better toleration. Clinical trials with larger samples are required to confirm these preliminary findings.

Keywords

Risperidone; divalproex; mania; bipolar; double- blind; randomized

INTRODUCTION

Pediatric bipolar disorder (PBD) resembles a more severe form of bipolar disorder in adults (1) with higher rates of substance abuse, academic failure, suicidal behavior and related psychosocial problems (2–5). Improved evidence-based treatment paradigms are urgently needed to alleviate the disabling symptoms of PBD and prevent the serious sequelae of this illness. Both the expert consensus treatment guidelines (6) and the Practice Parameters of the American Academy of Child and Adolescent Psychiatry (AACAP; 7) for treating PBD propose the use of “traditional mood stabilizers” such as divalproex sodium (divalproex) or lithium; or second generation antipsychotic (SGA), alone or in combination with a mood stabilizer for acute mania with or without psychosis. However, there is only a limited amount of preliminary evidence to support the use of mood stabilizers such as divalproex (8) or SGAs (9;10).

There are only three published, randomized trials in acute mania using divalproex treatment in this population (10;11). The first study compared divalproex with lithium and carbamazepine in acute mania and hypomania in 8 to 18 year olds and showed response rates of around 50% with all three agents (10). The second study was a double blind randomized trial comparing divalproex and quetiapine for an acute manic episode in 12–18 year old patients (11). There was no significant difference on the Young Mania Rating Scale (YMRS; 12) with a drop of 23 points on quetiapine and 19 points on divalproex. Remission rate, however, was significantly higher with quetiapine relative to divalproex. The slope of reduction in symptoms was also steeper in the quetiapine versus divalproex group. Within the group of bipolar adolescents with psychosis, quetiapine was significantly more effective than divalproex. Results from these two studies coupled with findings from open trials in pediatric mania showing that divalproex is useful (13–16), are in sharp contrast to those from the double blind placebo controlled (DBPC) trial of divalproex extended release (ER) showing no benefit relative to placebo (17). The DBPC trial reported a YMRS score reduction of 8.8 points with divalproex relative to 7.9 points on placebo (17). Further, divalproex was commonly associated with adverse effects such as gastrointestinal symptoms (e.g., abdominal pain, nausea, vomiting and diarrhea), tremors and sedation (15;16;18–21). The equivocal findings with divalproex require a well-designed trial comparing its efficacy to other promising drugs from alternative classes (e.g., SGAs) to determine the relative strengths and weaknesses of these treatments. This appears especially necessary given that two DBPC trials anti epileptic medications i.e., oxcarbazepine (22) and topiramate (23) yielded negative results in pediatric mania. In another trial that compared lithium, divalproex and placebo, divalproex lead to a significantly greater decrease in YMRS than placebo ($p<.01$), although lithium and placebo, or divalproex and lithium did not show significant difference in comparison, yielding equivocal results (24).

There is one completed, 3-week DBPC trial in pediatric mania that compared high dose risperidone (3 to 6 mg/day), low dose risperidone (0.5 to 2.5 mg/day) and placebo (25). The response rate ($\leq 50\%$ reduction in the baseline YMRS) and YMRS change scores were: 63%

and 16.5 points in the high dose group, 59% and 18.5 points in the low dose group, and 26% and 9.1 points in the placebo group, respectively. Significant improvement occurred in those who received risperidone versus placebo. There was no additional gain in doses greater than 2.5 mg of risperidone. There was significant weight gain among those on risperidone (irrespective of the dosage) when compared to placebo. In addition, two open label studies of risperidone in young patients (4 to 17 years of age) with manic, mixed, or hypomanic symptoms reported a 70% response rate (26;27). Among these open label studies, significant adverse effects included weight gain and prolactin elevation.

Based on the outcomes from the various clinical trials involving divalproex and risperidone, the available data do not support a strong preference for either drug in the treatment of pediatric mania. Therefore, we conducted a double blind randomized trial comparing divalproex and risperidone head-to-head to examine their relative efficacy and adverse event profiles. The results will contribute to constructing an evidence-based algorithm for treating acute manic and mixed episodes in PBD. Based on the existing data (10;11;25) with another SGA, quetiapine, we hypothesized that both divalproex and risperidone would be equally efficacious, but risperidone would produce a faster reduction in symptoms. We also predicted dissimilar adverse event profiles between the two groups, i.e., more gastrointestinal side effects with divalproex (15;16;19;21) and greater weight gain and elevated prolactin levels with risperidone (25–28).

METHODS

Design

This was a six-week double-blind, randomized outpatient treatment trial of risperidone plus placebo (that resembled divalproex capsule) vs. divalproex plus placebo (that resembled risperidone tablet) for manic episodes of PBD. Patients were assessed on weekly basis during the six week period, with ratings obtained at 7 time points. This study was approved by the University's Institutional Review Board (IRB) and subjects were recruited between June 2004 and January 2009. Parents and adolescents older than 16 years gave written permission and children younger than 16 years gave assent to participate in this trial.

Sample

Subjects were screened at our Pediatric Mood Disorders Program to determine if they qualified for the study according to the inclusion and exclusion criteria. Inclusion criteria were a DSM-IV diagnosis of bipolar disorder Type I (mixed or manic episode); 8 to 18 years old; and medication free or currently clinically unstable on medication, justifying termination of the ineffective regimen. To participate, subjects had to consent to being washed out of their current medications at study entry. The washout period consisted of tapering their previous medications, including stimulants, over one week prior to study entry, except for those receiving aripiprazole or fluoxetine who required a 4-week washout period. Exclusion criteria included: active substance abuse based on DSM-IV criteria (urine drug screen was completed for additional evidence through available laboratory tests i.e., amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates and PCP); serious medical problems; a history of allergy to risperidone or divalproex; and the presence of autism, nonaffective psychotic disorders, or any other psychiatric disorder requiring pharmacotherapy. One-hundred and eight potential subjects were initially screened. Attention Deficit Hyperactivity Disorder (ADHD) was included if present. Diagnosis of ADHD was made with reference to symptoms during the euthymic phase, reported by parents. The CONSORT Chart (Figure 1) illustrates the flow of the subjects with a total of 66 (risperidone group: n=33; divalproex group: n=33) of the initial 108 potential subjects participating in the study. Forty-two potential subjects did not meet the study criteria due to

a history of worsening on one of the two study medications (n=14); a diagnosis of bipolar disorder type II (N=5) or not otherwise specified (NOS) (n=15); use of cannabis (n=4); seizure history (n=2); and inability to comply with the scheduled visits required for the protocol (n=2). Thus, 66 subjects were randomized to the two treatment groups. One patient refused medication due to poor cooperation to comply with the protocol in taking medication after two days (patient was in the risperidone group). There were a total of 65 subjects that were treated and had follow-up data. Out of them, psychotic subtype of mania was present in seven subjects (22%) in risperidone group and six subjects (18%) in divalproex group. There were no significant between group differences on any of the demographic or clinical characteristics.

Study Medications

The study medications were administered in a double-blind, double-dummy randomized manner by our investigational pharmacist. Investigational staff involved in rating efficacy and safety measures, parents, caregivers and subjects were blind to the medication received. Risperidone was initiated at 0.25 mg to 0.50 mg per day. The dose was titrated to a maximum of 2 mg per day by increments of 0.25–0.5 mg every 2 days to achieve a maximum tolerable level by day 7. Divalproex was titrated up to 15 mg/kg/day over 3 days and serum level was measured at the end of 5 days. Divalproex dose was immediately adjusted on obtaining the serum level to aim for 80–120 µg/ml- trough, while ensuring that the dose was tolerated when increased. Serum valproate level was repeated at the end of the study. All medications and placebo pills were adjusted in “double-dummy fashion” by unblinded clinicians (JAC and TM). No dose adjustments were permitted for risperidone or divalproex after the first week, and fixed bid dosing schedule was used for consistency in estimating blood levels of divalproex across subjects. Benzotropine was allowed on as-needed basis for extrapyramidal side effects (EPS) in the risperidone group, and prescribed by the unblinded clinicians. In order to protect blindness, placebo tablets that resembled benzotropine were supplied by our investigational pharmacy for use in subjects receiving divalproex. Lorazepam at a dose of 1–2 mg (with a minimum of 4 hour gap between two doses), up to 4mg/day was allowed for a maximum of 3 consecutive days for acute states of mania associated with hyperarousal and severe agitation uncontrolled by study medications.

Assessment Procedures

All patients underwent a standard clinical assessment consisting of a diagnostic interview with the patient and family. In addition, each child and the parent or legal guardian were interviewed using the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS; 29). WASH-U-KSADS interviews were completed by MNP and TM, both of whom are board certified child psychiatrists, and a doctoral-level nurse practitioner in child psychiatry (JAC). Live diagnostic interviews of ten cases were coded by the three researchers to establish inter-rater reliability. By Cohen's *Kappa*, diagnostic inter-rater reliability for diagnosing any disorder using the WASH-U-KSADS was 0.94. Clinical information from all sources was combined and further discussed to resolve any diagnostic disagreement in a weekly consensus conference involving the research team (MNP, TM, JAC).

Efficacy Measurement

The primary efficacy measure was the YMRS. Secondary clinician-rated measures included the Child Depression Rating Scale-Revised (CDRS-R; 30), the Clinical Global Impression Scale for Bipolar Disorder (CGI-BP; 31), the Overt Aggression Scale (OAS; 32), and the Brief Psychiatric Rating Scale for Children (BPRS-C; 33). Parents completed the Child Mania Rating Scale (CMRS-P; 34). Three team members (EH, MM, SP), who have previously established inter-rater reliability for each of these rating scales, completed all

ratings on a weekly basis by interviewing the subject and his or her primary caregiver. Response for mania was defined as $\geq 50\%$ improvement from baseline on the YMRS and response for depression was defined as $\geq 50\%$ improvement on the CDRS-R. Given the mixed manic cases included in the sample, remission was defined as YMRS score of ≤ 12 , and CDRS-R score of ≤ 28 .

Safety and Tolerability Assessment

Physical examinations and laboratory assessments were obtained at baseline and the end of the study. Laboratory assessments included prolactin level, valproate serum level, calcium, phosphorous, uric acid, fasting glucose, total protein, albumin, liver function tests, thyroid function tests, creatinine kinase, electrolytes, urinalysis with drug screen, blood pregnancy test for females of child-bearing age, complete blood count (CBC), and electrocardiogram (ECG). Height, weight, blood pressure and heart rate were obtained on a weekly basis. At the time of designing the study, blood testing for bioavailable androgens (free testosterone) was considered in females if one of the following features was present: menstrual irregularities, obesity or hyperandrogenism (i.e., hirsutism and alopecia). EPS were assessed using the Abnormal Involuntary Movement Scale (AIMS; 35), Barnes Akathisia Rating Scale (BARS; 36), and the Simpson Angus Scale (SAS; 37). Further, adverse events were recorded using a comprehensive checklist developed by our research team (i.e., Pediatric Side Effects Check List, PSEC; 38). These adverse events were assessed every week by a research nurse in collaboration with subjects and their primary caregivers. The research nurse is employed by the general clinical research center (GCRC), and was specifically designated to rate adverse events, while the research assistants, blinded to the adverse events, completed the efficacy ratings.

Statistical Analysis

The relative efficacy of risperidone and divalproex were examined using two types of analyses. All the statistics presented in this study were derived from intent-to-treat analyses (39). First, we fit mixed-effects regression models using scores on the efficacy measures at all time points with all data on all subjects ($n=65$). Predictors were time, gender, active drug and the interaction between time and active drug. A quadratic term for time also was included, to model change over up to 7 waves of measurement. We evaluated the effects for the interaction between time and active drug to compare rates of change in symptoms associated with each drug. Next, we repeated the mixed model analyses using only those subjects who finished the entire study. We did this in order to assess any differences in the results due to attrition. Subjects' data were included in these models if they had a baseline assessment and at least one week of follow-up assessment.

RESULTS

Demographic and Clinical Characteristics

We report the demographic and clinical characteristics of the sample in Table 1.

Dosing of Risperidone and Divalproex Sodium

The mean (SD) risperidone dose at endpoint was 1.44 (0.56) mg/day in non-responders and 1.43 (.68) mg/day in responders. The mean (SD) divalproex dose at endpoint was 855.77 (215.58) mg/day (serum level= 96.3 $\mu\text{g/mL}$) in non-responders and 828.13 (359.03) mg/day (serum level= 95.8 $\mu\text{g/mL}$) in responders. The mean valproic acid level at end point was 96 $\mu\text{g/mL}$ and 92% of patients achieved a therapeutic valproic acid level by the 5th day and 100% by the study end point. Two subjects required dose adjustment on day 5 to reach the goal of $>80 \mu\text{g/mL}$ by day 7.

Two subjects in the risperidone group received benztropine (1 mg a day for 2 doses in one subject for jaw stiffness and daily for 4 weeks in one subject for akathisia). Placebo resembling benztropine was administered to one subject that was randomly selected by investigational pharmacist in the divalproex group for 4 weeks, to maintain the blind. Also, two subjects in the divalproex group and one subject in the risperidone group received lorazepam as a rescue medication.

Outcome on YMRS and CDRS-R

Means and standard deviations of all the measures at baseline, individual study endpoint, and Week 6 are reported by active drug in Table 2, along with laboratory parameters. In Table 2 we also report standardized mean difference effect sizes of change, within active drug group, using the baseline standard deviation of each measure. Based on dependent-samples *t*-tests and employing a Bonferroni correction to compensate for multiple tests, pre-post change in the risperidone group was significant for all measures except for OAS Suicidality. In the divalproex group, pre-post change was significant for the YMRS, CGI-BP Mania and Overall scores, OAS-Aggression and Irritability scores and on the CMRS-P. Similar patterns of statistical significance were found when the last observation was used (LOCF) and when analyses were limited to the sample that completed the study. A mixed-effects regression model of YMRS scores by active drug and time found evidence of more rapid improvement among those assigned to risperidone (slope = -8.29) compared to divalproex (slope = -7.12), indicated by a significant time by active drug interaction, $t(310) = 2.76, p < .01, d = .31$, but there was no significant difference in final LOCF or scores among completers at week 6. By contrast, the CDRS-R analysis found no significant difference in rate of change between risperidone (slope = -5.17) and divalproex (slope = $-4.16, t(311) = 1.84, ns, d = 0.21$), however LOCF scores on the CDRS were significantly lower for risperidone as compared to divalproex, $t(56) = 2.38, p < .05, d = .64$. Mean values of the YMRS and CDRS-R and standard errors are plotted by week in the panels of Figure 2.

The next set of analyses included only those subjects who completed the study, to gauge the sensitivity of the analyses to differences created by attrition within a small sample. This analysis also found evidence of more rapid improvement among those assigned to risperidone (slope = -9.68) compared to divalproex (slope = -8.27), with a significant time by active drug interaction, $t(231) = 3.19, p < .01, d = 0.42$. A similar analysis with the CDRS-R found no significant difference in rate of change between risperidone (slope = -5.24) and divalproex (slope = $-4.58, t(231) = 1.19, ns, d = 0.16$).

Finally, we employed repeated-measures analysis of variance to test differences in change from baseline to individual endpoints (LOCF). This analysis of the YMRS scores showed that those assigned to receive risperidone had greater baseline to endpoint change than those assigned to divalproex, $F(1,63) = 11.38, p < .01$. Similar findings were obtained in repeated measures analyses of the CDRS-R, $F(1,63) = 6.95, p < .05$, CGI-Mania, $F(1,63) = 11.68, p < .01$, the BPRS, $F(1,63) = 8.74, p < .01$, OAS-Aggression, $F(1,62) = 10.33, p < .01$, and OAS-Irritability, $F(1,62) = 7.89, p < .01$.

Response and Remission Rates

Response rates based on the YMRS were 78.1% for risperidone and 45.5% for divalproex using the individual endpoints of the study. This difference was significant, $\chi^2(1, N=65) = 7.33, p < .01$. Response rates based on the CDRS-R were 65.6% for risperidone and 42.4% for divalproex. This difference was marginal, $\chi^2(1, N=65) = 3.52, p < .10$. The remission rate for risperidone was 62.5%, compared with 33.3% for divalproex. This difference was significant, $\chi^2(1, N=65) = 5.54, p < .05$. Figure 3 illustrates the percentage of patients in

remission at each week over time in both the groups, and response and remission rates by drug are illustrated in Figure 4.

Outcome on Additional Efficacy Measures

Table 2 shows the ratings and the results of significance tests on the other efficacy measures, including the CGI Mania Severity Scale, the BPRS-C, the OAS Aggression, Irritability and Suicidality scales, and the CMRS-P. Mixed models of all these measures showed evidence for substantial improvement over time for all subjects, but no evidence for differential improvement by active drug. As the significance tests in Table 2 indicate, those assigned to risperidone had significantly higher baseline scores on the YMRS and the CGI-BP Mania subscale than those assigned to divalproex. However on the CGI-BP Overall Severity scale there was no difference between groups at baseline, at LOCF endpoint, or in completers at the end of six weeks. Pre-post change as assessed by a repeated measures ANOVA of the LOCF CGI-BP Overall Severity scores was substantial for both active drugs ($F(1,37) = 106.38, p < .001$), but did not differ significantly between them. Those assigned to risperidone also had significantly lower individual endpoint scores on the CDRS, CGI-BP Mania subscale, BPRS-C, and OAS Aggression subscale than those assigned to divalproex. There were no differences in outcome across groups, with or without psychotic subjects.

Safety and Tolerability

At study endpoint, a significantly larger number of subjects remained in the risperidone group ($n=25$) compared to that of divalproex group ($n=17$) ($\chi^2(1) = 5.03, p < .05$) (Figure 5). Reasons for premature discontinuation in the divalproex group were worsening in symptoms with increased irritability ($n=5$), lost to follow up ($n=2$), ineffective ($n=1$), depressed ($n=1$), suicidal ($n=1$), rash ($n=1$) and tics ($n=1$). Reasons for premature discontinuation in risperidone group were hospitalization and inability to continue in the trial ($n=1$), rash leading to emergency room visit and breaking of the blind ($n=1$), and refusal to take medication ($n=1$). There were no significant differences in reported weight gain, mean baseline-to-endpoint weight measurement, or weight gain over 7% of body weight in either group. Body mass index (BMI) at baseline, endpoint and change are reported in Table 2 and Figure 6. EPS presented in two subjects i.e., akathisia ($n=1$) and stiff jaw ($n=1$) in the risperidone group and none in the divalproex group. Regarding laboratory parameters, endpoint prolactin levels were greater in the risperidone versus divalproex group ($p < .05$) (Table 2). However, there were no clinically meaningful adverse effects reported due to the elevated prolactin levels in the risperidone group. There were no reported cases of sexual dysfunction in the study. There were no significant differences between the treatment groups in baseline to endpoint on changes on the ECG, liver function tests, thyroid function tests, creatinine kinase, electrolytes, CBC, vital signs or EPS. Clinical indication did not arise for us to measure free testosterone among female subjects as there were no reports of menstrual irregularities, obesity or hyperandrogenism.

Table 3 reports adverse events that were commonly reported, i.e., $\geq 10\%$ in either group. *Chi-square* tests found significant differences by active drug on reports of irritability/agitation, $\chi^2(1, N=65) = 7.61, p < .01$, and insomnia, $\chi^2(1, N=65) = 4.13, p < .05$, both of which subjects assigned to divalproex reported more frequently.

DISCUSSION

This is the first double blind randomized trial to compare divalproex with risperidone for the treatment of manic or mixed episodes in PBD. Our central finding supported our hypothesis that patients on risperidone improved more rapidly when compared to those receiving divalproex. This finding favors the choice of risperidone in acute mania for a more speedy

response. Also, contrary to our prediction, we found that risperidone showed significantly greater baseline-to-individual endpoint reduction compared to divalproex on the YMRS and other outcome measures. In addition, the YMRS response rate and the remission rate were also significantly greater with risperidone compared to divalproex. While there were no significant differences between groups in safety, greater number of patients continued to take risperidone for the full 6 week duration of the trial, compared to those receiving divalproex. Drop out rate was 24% in risperidone group and 48% in divalproex group, with increased irritability being the most common reason for drop out in the latter. Higher retention in risperidone group may also be due to reasons such as rapid and greater response in this group, although the current study cannot offer a definitive explanation for the lower rate of subject attrition in the risperidone group.

The onset of response is vital in an acute manic or mixed phase of PBD, as risks for impulsive, destructive and suicidal behavior are high during these episodes. Our results showing a more rapid reduction in symptoms with risperidone, as measured by the YMRS, when compared with divalproex, are consistent with a previous study that compared quetiapine with divalproex for treatment of PBD (10) and in adult studies of risperidone monotherapy (40). Another study in adult bipolar disorder that compared olanzapine, a SGA similar to risperidone and divalproex also indicated that olanzapine had faster onset of action relative to divalproex (41). Further, a retrospective chart review comparing risperidone with divalproex showed a faster decrease in symptoms with risperidone based on the CGI-Improvement Scale (42). Thus, our results support previous findings indicating that manic symptoms respond more rapidly to an SGA than a mood stabilizer.

Risperidone showed greater response than divalproex in treating symptoms of mania in PBD. The results on response rate with risperidone are similar to those reported in other studies of SGAs including studies of risperidone (25–27), olanzapine (26), aripiprazole (9), quetiapine (10) and ziprasidone (43). The 21.4 point drop in YMRS score with risperidone is comparable to the 23 point drop with quetiapine reported by DelBello et al. (10) using a similar design, and the 18.5 point drop reported by the DBPC trial of risperidone with similar doses to those of the present study (25). Similarly, an adult study that compared risperidone to placebo showed a reduction of 9.68 points among completers and 8.29 points among the group with LOCF (40). However, the drop in response to divalproex was much lower at 13 YMRS points in this study when compared to 19 points by DelBello et al (10). While the decrease in symptoms on YMRS with divalproex was much lower than with risperidone in our study, we found a greater response with divalproex (13 points) than was reported by Wagner et al.(8.8 points) (16), which did not differ from improvement of those on placebo. It is important to recall that our study did not have a placebo control arm. Analytic issues may explain the difference in the findings of these two studies. Wagner et al. (44), in their intent-to-treat analysis of efficacy, included all subjects who had at least one dose of divalproex, using last observation carried forward (LOCF) methods, whereas the present study excluded subjects who did not complete at least one weeks of post-baseline assessments and used mixed models (with all points of measurement) and repeated-measures analysis of scores between baseline and the study endpoint. In the Wagner et al. study (44), nearly one fourth of the subjects taking divalproex had discontinued divalproex before the end of the study. This could have made an effect more difficult to detect. In a Cochrane review of divalproex, using the outcome ‘failure to respond by the end of the trial,’ divalproex was found to be efficacious in adult studies relative to placebo (Relative risk ratio i.e., RR at .62; 45;46) and was comparable to lithium in the pediatric study (RR at 1.11; 11) of acute manic and hypomanic episodes. However, another important observation is that divalproex extended release (ER) form did not yield statistically significant improvement in mania symptoms in adult patients in a recent multi-site DBPC trial reported by Hirschfeld et al (47). It may be that the lower effect size in this study as well as that by Wagner et al (44)

may be due to the divalproex ER preparation for acute mania, as opposed to the immediate release form used in this study.

The more rapid rate of improvement with risperidone is clinically important to help patients quickly return to functioning at an optimal level. Even with a sample size of 65 subjects, we were able to show a robust and significantly greater decrease in YMRS symptoms with risperidone relative to divalproex. It is important to note that response with the low dose used in the DBPC trial of risperidone (25) and the mean dose used in our study (1.44 ± 0.56 mg) are comparable to the response with the high dose used in the DBPC trial (25). This suggests that there is no added advantage of using higher doses than 2.0 or 2.5 mg of risperidone in children and adolescents used in these studies. While the current sample is not sufficiently large to yield definitive results, our findings provide new information about the size of drug response that can be used to estimate the sample that will be required to better clarify the differences between these drugs.

Concerning psychosis, DelBello et al. (10) reported no difference in outcome when comparing quetiapine and divalproex on positive and negative symptom scores (PANSS; 48). Consistent with these results, we found that risperidone and divalproex were equally effective in reducing psychosis based on the BPRS-C scale change scores. Given the broad range of symptoms assessed with the BPRS-C, a more narrow measure that captures specific symptoms of psychosis in a larger sample size may better answer this question.

While it is important to sort out the effects of medications on aggression distinct from improvement in mania, previous studies demonstrate a steady reduction in aggression, impulsivity and irritability with divalproex (10;49) and risperidone (50). Using the OAS, we found a similar pattern of reduction in aggression and irritability with both medications, and no between treatment group absolute differences.

While there were no significant group differences in adverse effects, these results may be limited by the size of the sample and non-uniform occurrence of such events. Given that more patients on risperidone remained in the study compared with divalproex, it appears that risperidone may have been better tolerated, and this may be relevant in terms of patient adherence. Prolactin was increased more than three fold in risperidone group with no clinical adverse events such as breast enlargement or lactation and these results are similar to those reported by Biederman and colleagues in two open ended studies of risperidone (26;27). Prolactin elevation results from the antagonism of D2 receptors on the lactotrophs of the anterior pituitary, resulting in a disinhibition of prolactin release. Agents with the highest binding affinities for D2 (e.g., risperidone) result in the most substantial increases in prolactin levels (51). Treatment trials of risperidone in children and adolescents show acute elevations in prolactin, which peak and then regress to lower but still elevated steady-state levels after approximately 6–8 weeks of therapy. Significant elevations above 60 ng/mL are not uncommon (52). These, as well as long-term, studies reported by the manufacturer suggest that while prolactin elevation is significant and common, it does not always result in significant adverse-effects (e.g., galactorrhea, hirsutism, menstrual disturbances, decreased libido, etc) (53).

While neither group had patients that had significant weight gain, these results must be interpreted with caution due to small sample size in this study and in the light of other studies that reported greater weight gain, both with SGA and divalproex. In addition, lower weight gain, especially in risperidone group could be partially explained by the fact that this is a short-term out patient study requiring lower mean dose of medication in addition to lower mean baseline weight relative to divalproex group (although not significantly different). Among SGAs, weight gain was around 2 kg with 3 weeks of risperidone (54), 3.7

kg with 3 weeks of olanzapine (55), 0.55 kg with 4 weeks of aripiprazole (56), 1.7 kg with 3 weeks of quetiapine (57) and 1.0 kg with 3 weeks and 2.8 kg with 27 weeks of ziprasidone (58). In light of these findings, it is important to monitor for weight gain, glucose, and lipid parameters on regular basis (59). With regards to EPS, 6.3% of the subjects in the current study showed symptoms which is comparable to 8% in another study using a low dose of 0.5–2.5 mg of risperidone (54) and 12.2% on 10 mg dose of aripiprazole. Larger doses of risperidone (3–6 mg; 54) and aripiprazole (30 mg; 56) lead to higher incidence of EPS at 25% and 27.3% respectively. In contrast, quetiapine showed lowest incidence of EPS in PBD (10;57).

This study has limitations. Despite a sample size sufficient to detect drug treatment differences based on the YMRS-derived effect sizes, the sample size was not adequate to detect differential group differences on other indices, such as the parent-report CMRS-P or the clinician-rated aggression and psychosis measures. However, the parent ratings on the CMRS-P add the value of multiple informants, which reduce but do not eliminate the potential for bias. This was a “double-dummy” design, not a placebo-controlled trial comparing a single drug with placebo which may be necessary to definitively establish efficacy. Also, this is a short trial and extended use of either medication may have yielded definitive results. It cannot be generalized to inpatient population as it is an out patient trial with dose adjustments limited to the first visit. Finally and possibly related to the small sample size, differences by active drug in response and remission may be less definitive, with greater improvement suggested for those taking risperidone. As for the clinical implications, findings from this current study indicate that, second generation antipsychotic, i.e., risperidone may be a first option due to rapid response and greater reduction manic symptoms, when compared to an anti-epileptic, divalproex. In addition, with regards to tolerability, risperidone may be superior to divalproex, with no irritability or lesser gastro intestinal side effects with risperidone. Given that we found increased prolactin with risperidone, this may warrant close follow up for persistent high levels that could lead to emergence of adverse events such as sexual dysfunction, breast enlargement or lactation.

CONCLUSION

Our findings suggest that risperidone and divalproex demonstrate equal tolerability as monotherapy in the short term, for mania in children and adolescents. However, there was evidence that risperidone demonstrated more rapid onset of effect and a greater reduction in manic symptoms compared with divalproex. Discontinuation rate was higher in divalproex group relative to risperidone group. Larger samples and DBPC trials are required to confirm these preliminary findings.

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Figure 1.
CONSORT Chart of the Patient Flow in the Randomized Trial of Risperidone Versus
Divalproex in Pediatric Bipolar Disorder

Figure 2.
Clinical Symptom Response in Patients Treated with Risperidone and Divalproex

Figure 3.
Percent of Patients Achieving Remission by Week and Active Drug.

Figure 4. Response on YMRS and CDRS-R and Remission Rates by Active Drug. Note: YMRS = Young Mania Rating Scale. CDRS-R = Child Depression Rating Scale – Revised. Note: * $p < .05$.

Figure 5.
Subject Attrition by Active Drug

Figure 6.
Average Body Mass Index by Treatment Group

TABLE 1**Sample Characteristics of Patients by Treatment Group**

Variable	Mean (SD) or Frequency (%)		
	Risperidone (n=32)	Divalproex Sodium (n=33)	Total (N=65)
Mean age (Years)	10.47 (3.18)	11.23 (3.50)	10.85 (3.34)
Age Range (Years)	7–17.8	6.8–17.9	6.8–17.9
Mean (SD) Hollingshead SES	2.75 (1.25)	2.85 (1.27)	2.80 (1.20)
Gender (Male)	20 (62.5%)	19 (57.6%)	40 (59.7%)
Ethnicity			
African American	5 (15.6%)	4 (12.4%)	9 (14.1%)
Caucasian	20 (62.5%)	17 (51.5%)	37 (57.8%)
Hispanic	1 (3.1%)	0 (0.0%)	1 (1.6%)
Other or Unknown	5 (15.6%)	3 (21.2%)	8 (12.5%)
Mixed Episode at Baseline	11 (34.4%)	12 (36.4%)	23 (35.9%)
Manic Episode at Baseline	22(68.8%)	21(63.6%)	43(67.2%)
Rapid Cycling Illness	25 (78.1%)	27 (81.8%)	52 (81.2%)
Comorbid ADHD	7 (21.9%)	5 (15.1%)	12 (18.7%)
Comorbid Anxiety	4 (12.5%)	1 (3.0 %)	5 (7.8%)
Comorbid ODD/CD	3 (9.5%)	2 (6.1%)	5 (7.7%)
Psychotic features	7 (22%)	6 (18%)	13 (20%)
Medication Naïve Subjects	12 (37.5%)	14(39.4%)	26 (40%)
Antipsychotic Naïve Subjects	5 (15.6%)	8 (24.2%)	13 (20%)
Mood stabilizer Naïve Subjects	7 (21.9%)	6 (18.2%)	13 (20%)
Weight at Baseline			
Normal	30 (93.8%)	29 (87.9%)	59 (90.8%)
Over weight	2 (6.3%)	4 (12.1%)	6 (9.2%)

SES: Socio economic status; ADHD: Attention Deficit Hyperactivity Disorder; CD: Conduct Disorder; ODD: Oppositional Defiant Disorder

Table 2

Treatment Response to Risperidone or Divalproex Sodium and Laboratory Parameters

	Risperidone				
Scale Scores	Baseline Mean (SD) (n=32)	LOCF Mean (SD) (n=32)	Change E.S.	Week 6 (Completers) Mean(SD) n=25	Change E.S.
YMRS	30.59 (7.04)	10.22 (10.50)	-3.27 **	7.58 (8.28)	-2.89 **
CDRS	41.72 (17.44)	25.88 (9.13) *	-0.97 **	24.80 (8.65)	-0.91 **
CGI-BP Mania	4.97 (1.15)	2.34 (1.43) *	-2.55 **	2.04 (1.14)	-2.29 **
CGI-BP Overall	4.80 (1.06)	2.77 (1.28)	-2.57 **	2.08 (1.22)	-1.92 **
BPRS-C	34.41 (13.94)	11.84 (12.15) *	-1.73 **	10.28 (11.53)	-1.62 **
OAS-Aggression	16.16 (9.81)	3.00 (3.64) **	-1.37 **	2.72 (3.46)	-1.34 **
OAS-Irritability	6.58 (2.09)	2.61 (2.78)	-2.11 **	2.16 (2.70)	-1.90 **
OAS-Suicidality	1.19 (3.18)	0.03 (0.18)	-0.36	0.04 (0.20)	-0.36
CMRS-P	30.84 (10.87)	16.35 (13.09)	-1.51 **	14.38 (12.64)	-1.33 **
Dose (mg/day)	-	1.44 (0.72)			
SAS	0	0			
AIMS	0	0.24 (1.39)			
BARS	0	0			
Weight (lb)	81.12 (35.75)	80.19 (33.18)	Change (SD): .93 (-.3--8)		
Body Mass Index *	19.25 (4.62)	20.26 (4.73)	1.01		
Prolactin	7.18 (9.05)	26.08 (16.82) *			
ALK	203.82 (65.62)	208.83 (62.72)			
AST	28.41 (8.51)	27.56 (5.92)			

	Divalproex				
	Baseline Mean (SD) (n=33)	LOCF (n=33) Mean (SD)	E. S.	Week 6 (Completers) Mean (SD) (n=17)	E. S.
YMRS	25.09 (7.51)	15.24 (12.49)	-2.89 **	9.0 (9.5)	-4.35 **
CDRS	40.76 (13.34)	35.76 (15.01)	-0.91	28.8 (11.4)	-2.39
CGI-BP Mania	4.33 (0.89)	3.09 (1.42)	-2.29 **	2.4 (1.3)	-4.32 **

	Divalproex				
	Baseline Mean (SD) (n=33)	LOCF (n=33) Mean (SD)	E. S.	Week 6 (Completers) Mean (SD) (n=17)	E. S.
CGI-BP Overall	4.37 (0.67)	2.97 (1.50)	-1.92**	2.24 (1.09)	-4.53**
BPRS-C	31.21 (10.71)	22.12 (20.44)	-1.62	15.5 (24.1)	-2.47
OAS-Aggression	13.36 (25.09)	7.82 (7.18)	-1.34**	3.4 (4.2)	-1.65**
OAS-Irritability	5.70 (2.31)	3.82 (2.93)	-1.90**	2.2 (2.6)	-3.15**
OAS-Suicidality	0.55 (1.44)	0.30 (1.31)	-0.36	0.0 (0.0)	-0.37
CMRS-P	28.0 (9.02)	19.20 (12.66)	-1.33**	14.1 (12.1)	-2.84**
Dose (mg/day)	-	838.24 (260.58)			
SAS	0	0.			
AIMS	0	0			
BARS	0.09 (0.52)	0.09 (0.38)			
Weight (lb)	100.55 (57.47)	105.95 (56.17)	Change (SD): 5.4 (1- 7.3)		
Body Mass Index	21.81 (6.85)	22.22 (7.20)	0.41		
Prolactin	6.54 (4.77)	10.56 (5.39)			
ALK	186.58 (85.81)	175.92 (79.29)			
AST	25.53 (6.99)	24.92 (6.49)			

* $p < .05$;

** $p < .01$;

Notes: In columns labeled "Baseline," "LOCF," and "Week 6," asterisks refer to tests of differences between risperidone and divalproex within time point. In columns labeled "Change E.S.," asterisks refer to tests of the pre-post change within drug group; ALK = Alkaline phosphatase; AST = Aspartate aminotransferase; Effect Sizes (Change E.S.) are pre-post mean differences in baseline standard deviation units; LOCF = Last observation carried forward; SAS; Simpson-Angus Scale; AIMS: Abnormal Involuntary Rating Scale; BARS: Barnes Akathisia Rating Scale

Table 3

Common Treatment- Emergent Adverse Events (N=65)

Variable	Frequency (%)	
	Risperidone (n=32)	Divalproex Sodium (n=33)
Increased appetite	8 (25.0%)	10 (31.3%)
Irritable/agitated	0 (0.0%)	7 (21.9%) *
Stomach discomfort	6 (18.8%)	5 (15.6%)
Sleepiness	5 (15.6%)	4 (12.5%)
Fatigue/tiredness	5 (15.6%)	4 (12.5%)
Insomnia	0 (0%)	4 (12.5%)
Weight gain	3 (9.4%)	4 (12.5%)

*
 $p < .05$ for comparison of Divalproex vs. Risperidone