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A Head-to-Head Comparison of Risperidone and Divalproex for Treatment of Pediatric Bipolar Disorder

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Introduction

There are distressingly few well-controlled clinical trials of psychopharmacologic interventions for childhood psychiatric disorders. Pediatric bipolar disorder (PBD), while the subject of some nosologic controversy [1], is in its “pure” form a devastating relapsing/remitting disorder that can be very difficult to treat. This National Institutes of Health–supported trial (medication and placebo capsules supplied without cost by the respective manufacturers of risperidone and divalproex) is a welcome addition to the literature, as it compares two of the most commonly recommended medications for mania in PBD, neither of which has a substantial evidence base supporting its use for that indication.

Aims

The study compared the 6-week efficacy of placebo plus risperidone with that of placebo plus divalproex (the pairs of pills appeared the same in each arm) in a randomized, double-blind trial.

Methods

Sixty-six children ($n=33$ per treatment group) between 8 and 18 years of age who met *DSM-IV* criteria for bipolar disorder, mixed or manic type, were randomly assigned to one of the treatment groups after a minimum of 1 week of washout of other medications (4 weeks for fluoxetine or aripiprazole). Patients with an additional diagnosis of attention-deficit/hyperactivity disorder were included, but medications targeting that disorder were also discontinued. The study excluded those with comorbid substance use disorders, medical complications, or relevant medication allergies. PBD with psychotic features occurred in seven (22%) and six (18%) patients in the risperidone- and divalproex-treated groups, respectively, and the demographics of the groups did not differ significantly. Risperidone was titrated to doses between 0.25 and 2 mg/d in 0.25-mg increments every 2 days, and divalproex doses were titrated to 15 mg/kg per day over 3 days, and then adjusted to maintain trough serum levels between 80 and 120 $\mu\text{g/mL}$. The primary efficacy measures were scores on the Young Mania Rating Scale (YMRS) [2], and depression symptoms were rated as secondary outcomes by the Child Depression Rating Scale-Revised (CDRS-R).

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Rating: • Of importance.

Disclosure

No potential conflict of interest relevant to this article was reported.

Results

Sixty-five patients underwent sufficient treatment to provide data, with one dropping out of the risperidone group as a result of nonadherence after 2 days. Although both medications resulted in improvement in YMRS scores, risperidone did so more rapidly, as indicated by a significant time–drug interaction term in the main regression model. By some secondary outcome measures, risperidone appeared to result in greater improvement (eg, lower final score on the CDRS-R assessed with last observation carried forward) and also appeared to yield a treatment response (defined as $\geq 50\%$ improvement in YMRS for mania and CDRS-R for depression, respectively) in a larger proportion of patients (78.1% responders vs 45.5% responders for YMRS; 65.6% vs 42.4% for CDRS-R). Attrition was significantly lower in the risperidone group (25 completers for risperidone vs 17 for divalproex). Weight gain was modest ($\leq 7\%$ of baseline weight) for both drugs. Two of the risperidone-treated patients experienced extrapyramidal effects necessitating administration of benztropine. Adverse events included irritability and insomnia and were more frequent in the divalproex group.

Discussion

The authors concluded that risperidone overall was preferable to divalproex as a single-agent therapy in this small but well-designed study. They noted the clinical importance of achieving as rapid a response as possible in manic or mixed-episode patients, and rate of response was among the measures for risperidone that appeared superior. The authors appropriately call for additional larger studies of pharmacologic therapies in PBD.

Comments

Despite its small size, this is an important study, as it builds confidence in risperidone as a first-line medication for mania in PBD. Given the substantial teratogenic risks associated with use of valproate during pregnancy [3], it is particularly useful to have some evidence that presumably safer alternatives are available for reproductively competent female patients with PBD. It was reassuring that weight gain was minimal in this study for both medications, but it is important to note that with a duration of only 6 weeks, this trial is not adequate to evaluate weight gain.

References

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