Risperidone vs Divalproex in Bipolar Disorder

In a head-to-head clinical trial of pediatric bipolar disorder, risperidone was more effective, worked more rapidly, and was better tolerated than divalproex.

Methods: The trial, sponsored by the NIH, was conducted as part of a project to develop an evidence-based algorithm for treating acute mania and mixed states in children and adolescents. Patients with bipolar I disorder who were experiencing a manic or mixed episode were eligible, provided they were medication free or on an ineffective regimen, which was to be terminated at study entry. Participants (mean age, 11 years) received double-blind randomized treatment with either risperidone, titrated to a maximum of 2 mg/day (mean, 1.4 mg/day), or divalproex, titrated to a serum level of 80–120 mcg/mL (mean, 96 mcg/mL). Dose adjustments were not permitted after the first week. Patients were treated for 6 weeks and evaluated at weekly intervals. The primary efficacy measure was the Young Mania Rating Scale (YMRS).

Results: Sixty-five patients entered the study and received at least 1 week of treatment. Compared with baseline, average YMRS scores were significantly decreased in both treatment groups, but the magnitude of improvement was greater and it occurred more rapidly with risperidone. The rate of mania response, defined as a ≥50% decrease in the YMRS score, was 78% for risperidone, compared with 46% for divalproex (p<0.01). Rates of remission (YMRS score of ≤12) were 63% and 34%, respectively (p<0.05).

Secondary outcome measures, which included rating scales for depression, overall illness severity, aggression, and parent-rated mania, did not differ between the groups. Results were similar when all subjects were compared using the last observation carried forward* (LOCF) method, and when the analysis was limited to those who completed 6 weeks of treatment.

Six patients in the risperidone group and 16 in the divalproex group did not complete the planned 6 weeks of treatment. Of note, 5 patients withdrew from divalproex treatment because of worsening symptoms and increased irritability, and another because of treatment ineffectiveness. The groups did not differ in weight gain, an unexpected result because weight gain is often reported with second-generation antipsychotics, but the duration of treatment was short.
Prolactin levels were markedly increased in the risperidone group, but did not result in clinically significant side effects. Extrapyramidal symptoms occurred in 2 risperidone-treated patients.

**Discussion:** This clinical trial was the first double-blind comparison of risperidone and divalproex in pediatric bipolar disorder. The results should be regarded as preliminary. Based on other evidence, risperidone was expected to work more rapidly than divalproex, but the finding of greater overall efficacy was unexpected.

**Study Rating*—17 (100%):** This study met all criteria for a randomized controlled trial.

Pavuluri M, Henry D, Findling R, Parnes S, et al: Double-blind randomized trial of risperidone versus divalproex in pediatric bipolar disorder. *Bipolar Disorders* 2010:12 (September):593–605. From the University of Illinois at Chicago; and other institutions. Funded by the NIH. Several study authors disclosed commercial relationships with pharmaceutical-industry sources.

Drug Trade Names: divalproex sodium—Depakene, Depakote; risperidone—Risperdal

*See Reference Guide.

### Predictors of Adolescent Suicide

Because a previous suicide attempt is a strong predictor of completed suicide, identifying risk factors in adolescent populations with a recent attempt could improve treatment and prevention strategies.

**Methods:** Data from the 2007 Youth Risk Behavior Survey, conducted in a weighted nationally representative sample, was used to assess risk factors for suicide among high school students and to determine if gender differences exist. More than 14,000 students completed anonymous, self-administered questionnaires evaluating the presence of 14 potentially associated psychosocial risk factors, as well as 12-month history of suicide attempts.

**Results:** Overall, 6.9% of adolescents attempted suicide. Attempts were more common among girls than boys (9.3% vs 4.6%; odds ratio* [OR], 2.9). Among girls, significant associations with suicide attempts were found for self-reported sadness (OR, 5.7); huffing glue (OR, 2.0); forced sex (OR, 1.7); dating violence (OR, 1.60); and weapon carrying (OR, 1.5). Sadness (OR, 11.0), forced sex (OR, 2.6), weapon carrying (OR, 1.7), and huffing glue (OR, 1.6) also predicted suicide attempt in boys, as did hard drug use (OR, 2.2) and sports involvement (OR, 1.5). Girls in 9th or 10th grade were nearly twice as likely as older girls to attempt suicide (OR, 1.8), but age did not appear to affect risk in boys.

**Discussion:** This survey highlights the importance of sadness, substance abuse, and violent victimization as particularly strong predictors of suicide attempts in adolescents. Additional gender-specific factors that should be considered in prevention efforts include dating violence and younger age in girls, and hard drug use and sports involvement in boys.


*See Reference Guide.

### Preliminary Report on the Safety of Riluzole in OCD

Riluzole inhibits presynaptic glutamate release and enhances reuptake of glutamate by glial cells. It is FDA approved only for treatment of amyotrophic lateral sclerosis, but preliminary evidence has suggested it may be effective in adults with major depressive disorder and anxiety and in both adults and children with OCD.

In a small open-label trial of children, aged 8–17 years, who received adjunctive riluzole, the mean Children’s Yale-Brown Obsessive Compulsive Scale decrease was 39%, and 4 of the 6 patients...
achieved Clinical Global Impression-Improvement (CGI-I) ratings of "much improved" or "very much improved." Based on these positive results, a double-blind placebo-controlled trial is being undertaken in children aged 7–17 years with moderate-to-severe OCD that has not responded to conventional treatment. Patients are randomized to receive 12 weeks of 50 mg riluzole b.i.d. or placebo and may elect at the end of 12 weeks to receive open-label riluzole. Subjects will be followed at the NIH for 1 year. Thus far, 46 of a planned 60 patients have been enrolled. However, a preliminary safety review has been completed.

Riluzole has been generally well tolerated in these patients; few have discontinued treatment and all who completed 12 weeks elected to take open-label riluzole. Transaminase elevations caused several patients to discontinue double-blind treatment, but the patients were all offered and received open-label treatment without further incident. One patient with known steatosis of the liver stopped open-label treatment because of a transaminase elevation. Pancreatitis developed in 2 of the 46 patients, but 1 was taking 3 concomitant medications and the other was found to have an elevated serum riluzole level presumed to be associated with concomitant fluvoxamine use. Pancreatitis has been reported rarely in adults treated with riluzole.

Based on these preliminary data, the authors conclude "if riluzole proves effective for psychiatric conditions, including conditions in childhood, then it may be used as monotherapy in the future with an acceptable safety profile." The present study is still underway, and outcome data will be released upon completion.


**Drug Trade Names:** fluvoxamine—Luvox; riluzole—Rilutek

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### Secondary Intervention to Prevent PTSD

A brief intervention reduced stress and anxiety symptoms in children and adolescents at risk for posttraumatic stress disorder.

**Background:** The Child and Family Traumatic Stress Intervention (CFTSI) is a manualized therapy designed for use in children aged 7–17 years who have recently experienced a traumatic event. Consisting of four 90-minute sessions, it is delivered to both patients and their primary caregivers. The CFTSI has 2 main focuses: increasing communication between the child and caregivers in an effort to increase the caregivers’ support of the child; and teaching specific behavioral skills to cope with symptoms such as sleep disturbance, intrusive thoughts, and avoidance.

**Methods:** This pilot study enrolled 106 youth (mean age, 12 years) referred to an urban child mental health clinic. Participants had experienced a potentially traumatic event and had onset of at least 1 new PTSD symptom within 30 days after the event. Because the baseline interview had to be administered within 30 days of the exposure, patients could not, by definition, meet criteria for a PTSD diagnosis. Precipitating traumas included motor vehicle crashes (24%), physical assaults (21%), witnessing violence (19%), and sexual abuse (18%), plus injuries, animal bites, and threats of violence. Participants were randomly assigned to receive either the CFTSI or a 4-session psychoeducational intervention that also involved the caregivers to a similar extent. Symptom severity on the Trauma Symptom Checklist for Children (TSCC) and presence of a full or partial PTSD diagnosis were measured 3 months after the end of treatment.
Results: Compared with children who received the control intervention, those who received the CFTSI showed significantly greater improvement on the posttraumatic stress and anxiety indices of the TSCC (p ≤ 0.04). CFTSI was also associated with a lower likelihood of meeting full or partial diagnostic criteria for PTSD at 3 months, although the number of participants who did meet diagnostic criteria was not reported. Among PTSD symptoms, patients who received the CFTSI reported significantly less re-experiencing and avoidance than controls, but not less hyperarousal.

A limitation of this study is the high attrition rate: of 176 families referred, 64 failed to attend their evaluation appointment and 15 more did not receive any treatment. High attrition rates are common in urban child mental health clinics. The children had an average of 6 prior traumatic events, which suggests the CFTSI may have been treating established PTSD rather than preventing its onset.

Discussion: Although preliminary, these results suggest a brief early intervention administered soon after a traumatic event may prevent the development of chronic PTSD. A primary focus of the intervention should be enhancing emotional support by an adult caregiver.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial, but neither patients nor evaluating clinicians were blinded to treatment assignment.


*Reference Guide Item.

Fluvoxamine-Associated Disinhibition

Reported adverse effects of SSRIs in young patients include behavioral activation, manic symptoms, and increased risk of suicidal thoughts. Because several SSRIs, including fluvoxamine, have been associated with disinhibition, a retrospective chart review was undertaken to examine its occurrence with fluvoxamine in a clinical sample of patients with OCD. Charts
were reviewed for all patients treated at an anxiety disorders clinic over a 7-month period. A total of 51 patients were treated for OCD; 17 (33%) with fluvoxamine. Of these 17 patients, 3 experienced disinhibition within 9 months of starting treatment.

The first patient, a 12-year-old male, had previously experienced behavioral activation with fluoxetine and had been unable to tolerate mirtazapine. Within 6 weeks of starting fluvoxamine, which was titrated to 150 mg/day, he became impulsive, oppositional, and aggressive and displayed poor judgment by engaging in dangerous activities. Symptoms resolved when fluvoxamine was stopped and he has had no recurrence with low-dose sertraline. The second patient, an 11-year-old male with comorbid OCD, ADHD, and a chronic motor tic, had undergone multiple failed medication trials before 25 mg/day fluvoxamine was added to ongoing clomipramine, risperidone, and bupropion. Within 1 month, he exhibited disinhibited behavior and was angry and disrespectful. Impulsiveness resolved with fluvoxamine discontinuation. The third patient, a 10-year-old male, was diagnosed with OCD and Tourette’s disorder. After 9 months of treatment with 50-mg fluvoxamine b.i.d. he began to exhibit uncharacteristically impulsive behavior. He was switched to sertraline, which also produced disinhibition. He was referred for cognitive-behavioral therapy.

Pharmacogenetic testing was undertaken in all 3 patients. Two of the boys were found to be extensive metabolizers of both cytochrome P450 2C19 and 2D6 and should theoretically have been able to tolerate full-dose treatment. Both, however, experienced disinhibition with low-dose therapy. The third boy extensively metabolized CYP2C19, but was a poor 2D6 metabolizer, which leads to higher-than-expected medication exposure.

The present case series serves as a reminder of SSRI-associated disinhibition, particularly in patients with altered CYP metabolism. Disinhibition is an important adverse effect because associated behaviors can often put patients in danger.

Harris E, Eng H, Kowatch R, Delgado S, et al: Disinhibition as a side effect of treatment with fluvoxamine in pediatric patients with obsessive-compulsive disorder. *Journal of Child and Adolescent Psychopharmacology* 2010;20 (August): 347–353. From Cincinnati Children’s Hospital Medical Center; and the University of Cincinnati Medical School, Ohio. Two study authors disclosed commercial relationships, including speakers bureau participation, with pharmaceutical-industry sources.

Drug Trade Names: bupropion—Wellbutrin; clomipramine—Anafranil; fluoxetine—Prozac; fluvoxamine—Luvox; mirtazapine—Remeron; risperidone—Risperdal; sertraline—Zoloft

## Treating Externalizing Behavior

Parent-Child Interaction Therapy (PCIT) is a parent training intervention for disruptive behavior that has been studied primarily in research settings. Most research on PCIT has been conducted in Caucasian families seen in hospital or university clinics. The present study was carried out in an urban community mental health center, and results were mixed. While effective in families who completed treatment, success was hampered by high attrition.

**Background:** PCIT is a manualized intervention consisting of 2 phases. In the Child-Directed Interaction phase, parents are coached during observed interactions on how to respond to their child in ways that improve play therapy skills and support social interaction, and on increasing positive parent behaviors, such as praising the child. The Parent-Directed Interaction phase builds on these skills by introducing unambiguous parental commands, limit-setting, and consequences to the child for disruptive behavior.

**Methods:** Participants were 14 families with a child who met diagnostic criteria for a disruptive behavior disorder. In 12 families, the participating caregiver was a single mother. Children in the study had a mean age of 4 years (range, 2–7 years); 7 were African-American, 4 were multiracial, and 3 were Latino. PCIT sessions lasted 90 minutes each and were continued until
dropout or until scores on the parent-rated Eyberg Child Behavior Inventory (ECBI) dropped to near the normative mean and the parent and therapist agreed that the parent could manage the child’s behavior. Extra efforts were made to reduce barriers to treatment, such as providing transportation vouchers and continuing to see patients with high no-show rates.

**Results:** Two families attended an assessment session but did not receive any treatment. Outcomes were analyzed in the remaining 12 families. Four families completed treatment, reaching therapeutic goals after an average of 14 sessions. The remaining families withdrew after a mean of 6 sessions, without meeting treatment goals. Of 4 self-referred families, 3 were among those who successfully completed treatment. Those referred by schools or agencies were less likely to complete treatment.

The 4 treatment completers showed a steady decrease in ECBI scores over time, finishing well below the completion criteria. Dropouts showed less change, but 4 of these 8 families also met the numeric cutoff for success. The 4 families that completed treatment showed substantial reductions in standardized measures of disruptive behavior, parenting stress, and child functioning. (These data were unavailable for non-completers.)

Parents indicated a high degree of treatment satisfaction on a rating instrument, although there were occasional comments to therapists suggesting cultural incongruities between PCIT and ethnic minorities' parenting styles.

**Discussion:** Despite the treatment gains, the high attrition rate in the study highlights the difficulties of providing services to urban, minority families with low socioeconomic status. The differences in dropout rates between self-referred and mandated participants calls into question the usefulness of the PCIT intervention in families who do not voluntarily enter treatment. In addition, the gains demonstrated by families who discontinued before completing the intervention raise the question of how much treatment is necessary for difficult-to-engage families. Future study should include specific interventions to enhance treatment engagement.

Lyon A, Budd K: A community mental health implementation of Parent-Child Interaction Therapy (PCIT). *Journal of Child and Family Studies* 2010;19:654-668. From DePaul University, Chicago, Ill., and the University of Washington, Seattle. Funded by DePaul University; and other unnamed sources. The authors did not include disclosure of potential conflicts of interest.

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**Reference Guide**

**Last Observation Carried Forward (LOCF):** A method of data analysis in which missing data for individual patients is replaced by the last observed value of that variable.

**Odds Ratio:** A comparison of the probability of an event in two groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**Study Rating:** A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists have been posted at www.alertpubs.com.

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