Risperidone vs. Valproic Acid in Preschool Bipolar Disorder

In a small randomized trial, risperidone was clearly superior to placebo in young children with bipolar I disorder, while valproic acid was not. Children were highly sensitive to the adverse effects of both medications, suggesting a need for frequent monitoring.

**Methods:** The study enrolled 46 patients, aged 3–7 years, with bipolar I disorder, experiencing mixed or manic episode. Patients with comorbid ADHD were included. After a washout of prior medications, including stimulants, patients received treatment for 6 weeks with randomly assigned, double-blind risperidone, valproic acid, or placebo. Risperidone was flexibly dosed (mean dosage, 0.5 mg/day; range, 0.5–0.75 mg/day). The valproic acid dose was adjusted to target blood levels of 80–100 mcg/mL (mean dosage, 300 mg/day). A total of 18 patients received risperidone, 21 valproic acid, and 7 placebo. Response was defined as a ≥50% decrease in Young Mania Rating Scale (YMRS) total score or a Clinical Global Impression–Improvement (CGI-I)* rating of 1 or 2.

**Results:** Mean baseline YMRS scores were 30 in the valproic acid group, 32 in the risperidone group, and 31 in the placebo group. After 6 weeks of treatment, risperidone was associated with a significant decrease from baseline in mean YMRS score (-19 points; p=0.001), while the other treatments were not (valproic acid, -10 points; placebo, -4 points). Risperidone was significantly superior to both placebo (p=0.008) and to valproic acid (p=0.004) with regard to the final YMRS score, while valproic acid did not differ from placebo. Effect sizes* were 3.58 for risperidone, 1.66 for valproic acid, and 0.56 for placebo. Final CGI-I ratings indicated treatment response in 88% of the risperidone group (p=0.003) and 50% of the valproic acid group (p=0.008), and no placebo patients. The hazard ratios* for a ≥50% decline in YMRS score, relative to placebo, were 6.97 for risperidone and 1.95 for valproic acid. Risperidone-treated patients demonstrated clinical response by weeks 2–3, while valproic acid response was not evident until weeks 4–5.

One child discontinued valproic acid because of nausea, and 2 others because of anger outbursts. No patient discontinued risperidone or placebo because of an adverse event associated with
study medication. Both active medications were associated with weight gain and increased body mass index. Treatment with valproic acid was associated with decreases in the total red blood cell count, hemoglobin, and hematocrit, while risperidone was associated with increased prolactin levels and adverse changes in liver function and cholesterol. None of the laboratory changes were clinically significant, but the time span of the study was brief.

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


From the Ohio State University Wexner Medical Center/Nationwide Children's Hospital, Columbus; and other institutions. **Funded by the Stanley Medical Research Foundation. The study authors declared no financial relationships with pharmaceutical sources.**

*Drug Trade Names:* risperidone—*Risperdal*; valproic acid—*Depakene, Depakote*

*See Reference Guide.*

## Mortality in ADHD

According to results of a longitudinal cohort study, mortality is increased more than 2-fold in children, adolescents, and adults with ADHD. The increase observed in this study was driven largely by deaths from unnatural causes, with accidents the most common cause.

**Methods:** The study cohort included nearly 2 million children who were born in Denmark between 1981 and 2011. Data on ADHD and other comorbid diagnoses of interest were obtained from national registry records and from patient contacts with departments of psychiatry, pediatrics, and neurology through 2013; data from outpatient visits were only available for primarily the latter half of the study period. The main outcome was all-cause mortality after the age of 1 year. Maximum age at end of follow-up was 32 years. Unnatural causes of death (i.e., homicide, suicide, accident, or undetermined) were a secondary outcome.

**Results:** More than 32,000 members of the birth cohort received a diagnosis of ADHD during follow-up. Mean age at diagnosis was 12 years. Among persons with ADHD, 17% had a comorbid diagnosis of oppositional defiant disorder or conduct disorder, and 12% had a substance use disorder.

During follow-up, 107 persons with ADHD died. The mortality rate in ADHD was 5.85 per 10,000 person-years, compared with 2.21 in persons without ADHD, for an adjusted mortality ratio* of 2.07 (p<0.0001). Excess mortality in those with ADHD was greatest in patients who received their diagnosis after the age of 17 years (fully adjusted mortality rate ratio, 4.25; p<0.0001). Excess mortality related to ADHD was also greater in women and girls than in men and boys, although the difference was not statistically significant. Comorbid disorders significantly increased mortality. Compared with cohort members with no ADHD, adjusted mortality ratios were 1.5 for those with ADHD alone, 2.17 for those with ADHD plus oppositional defiant disorder/conduct disorder, 5.63 for those with ADHD plus substance use disorder, and 8.29 for those with all 3 comorbid conditions.

Of the 79 patients with ADHD for whom information on the cause of death was available, the cause was unnatural in 54 (68%); 42 of the deaths were the result of an accident. Rates of death from both natural and unnatural causes were elevated in persons with ADHD.

**Discussion:** This appears to be the first large-scale, long-term study of mortality in ADHD. Earlier studies have shown that ADHD is associated with greater risk of serious traffic accidents, substance use disorder, criminality, and more severe mental disorders that can affect life expectancy. Certain comorbid conditions increased mortality in the present study population but did not fully explain it.
The observation that girls and women with ADHD had greater mortality than boys and men suggests that the diagnostic threshold may be higher in females, resulting in a population with more severe and impairing symptoms, or that they may be less likely to receive treatment. The study results emphasize the importance of early identification of ADHD, especially in girls, and of treatment of comorbid oppositional defiant, conduct, and substance use disorders.


*See Reference Guide.

**Timing of SSRI Response**

In children and adolescents, the bulk of the antidepressant response to SSRI therapy occurs within the first 2–4 weeks of treatment, according to a meta-analysis. This study, the first meta-analysis to analyze treatment effects on a week-to-week basis, suggests there may be little benefit of prolonged treatment trials as is currently recommended.

*Methods:* A literature search identified published, randomized, placebo-controlled trials of SSRIs for short-term treatment of pediatric unipolar depression. Included trials provided weekly data points and used a validated symptom scale as the primary efficacy measure. The meta-analysis included 13 trials with a total of 3004 child and adolescent patients. There were 5 trials of fluoxetine, 3 of paroxetine, 1 of sertraline, and 2 trials each of citalopram and escitalopram.

*Results:* A statistically significant benefit of SSRI therapy relative to placebo was evident as early as 2 weeks after the start of treatment. By treatment week 2, 69% of all improvement had already occurred, and nearly all of the additional benefit was evident by week 4. No significant treatment effect of maximum SSRI dose was found. There were no differences among individual SSRIs, and no differences related to patient age or between children and adolescents. Trials published in later years were associated with a smaller treatment effect relative to placebo than earlier trials. Industry funding had no effect on results. Compared with the published literature in adults, children and adolescents experienced a smaller treatment benefit from SSRI therapy (p<0.0001), even when controlling for drug dosage.

*Discussion:* These data suggest the currently recommended 2-month treatment trials of SSRI therapy in pediatric depression may be unnecessary if treatment outcome can be predicted by response at week 2 or 4. There also appears to be no benefit of increasing doses within the therapeutic range of an SSRI. The weaker response to SSRIs in children than in adults may reflect truly lower efficacy in younger patients or it could be explained by potential attributes of pediatric trials, such as reduced sensitivity in measuring decreasing symptoms of depression.

*Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis. However, individual study quality does not appear to have been assessed.


Drug Trade Names: citalopram—Célexa; escitalopram—Lexapro; fluoxetine—Prozac; paroxetine—Paxil; sertraline—Zoloft

*See Reference Guide.
**Trends in Adolescent Self-Injury**

The number of emergency department (ED) visits for self-injuries in adolescents increased between 2009 and 2012, according to an analysis of national trauma data. The analysis identified specific subgroups of adolescents that may benefit from increased prevention efforts, including those with public insurance or no insurance and those with comorbid conditions.

**Methods:** Investigators analyzed records of the National Trauma Data Bank, which collects data from >700 U.S. hospitals, including nearly all Level I and Level II trauma centers. The study data spanned from 2009 to 2012 and included patients aged 10–18 years. Change over time in rates and methods of self-injury as well as potential risk factors were evaluated. However, data limitations did not allow for determination of whether the injuries were inflicted with suicidal intent.

**Results:** Of nearly 287,000 ED visits for trauma in adolescents, 3664 (1.3%) were for self-injury. Patients with a self-injury were more severely injured and had higher rates of multiple comorbid conditions. However, <5% of patients with self-injury had a psychiatric diagnosis. The proportion of visits for self-injury increased from 1.1% in 2009 to 1.6% in 2012 (p<0.001). Cutting/piercing was the most common mechanism of self-injury. There was a significant decrease in firearm injuries as a fraction of the total, from 27% to 22% (p=0.02). The risk of self-injury, relative to other causes, was increased in girls; older adolescents (≥15 years); those with comorbid conditions; those with public insurance or no insurance; and those with alcoholism or obesity. Adolescents most likely to die of their injuries were male, older, white, and lacking insurance coverage.

**Discussion:** Most children and adolescents treated in the ED for self-injury do not die; however, they are at very high risk for a subsequent successful suicide attempt, with the greatest period of risk occurring immediately after that episode. Since 2009, few studies have examined the epidemiology of adolescent self-injury. New trends include the decrease in self-inflicted firearm injuries, possibly the result of strategies to reduce access to firearms, and the apparent shift to cutting and piercing. The low number of patients with a diagnosed mental illness was a surprising finding that may reflect missed opportunities to document mental health problems and link patients to care.


**Prenatal SRI Exposure and Childhood Behavior**

In a longitudinal study, children exposed to serotonin reuptake inhibitor antidepressants in utero had increased internalizing behaviors and anxiety at school entry age.

**Background:** During development, serotonin plays a key role in neuronal proliferation, differentiation, migration, and synaptogenesis. Although SRIs are known to cross the placenta and there is substantial experimental evidence of adverse developmental effects in animals, there have been few studies to research the effects of prenatal SRI exposure on childhood outcomes.

**Methods:** Study participants were 110 mother-child pairs, recruited during the second trimester of pregnancy, for whom complete follow-up data were available on child behavioral outcomes at the ages of 3 and 6 years. In 44 of the pregnancies, the mother took an SRI from the time of conception and typically for all or most of the pregnancy. Child outcomes
were assessed by the mother using the Child Behavior Checklist (CBCL) at age 3 years and the MacArthur Health and Behavior Questionnaire (HBQ-P) when the child was 6 years old. Maternal anxiety and depression were also assessed throughout pregnancy and follow-up.

**Results:** Children exposed to SRIs prenatally were more likely than those who were not exposed to be born preterm (14% vs. 3%; *p* = 0.036), and they were born at an earlier gestational age (39 vs. 40 weeks; *p* = 0.001). These children were also smaller than average and had lower Apgar scores.

Exposed children had higher levels of internalizing behaviors and anxious/depressed symptoms at ages 3 years and 6 years than unexposed children. They were more likely to meet clinical thresholds for internalizing behaviors at age 3 (16% vs. 1.5%; *p* = 0.004) and at age 6 (14% vs. 3%; *p* = 0.036). The 2 groups did not differ with regard to externalizing behavior or attention.

Current maternal depression when the child was aged 3 or 6 years was also significantly associated with increased internalizing, externalizing, and anxious behavior at those ages. However, in a multivariate model, in-utero SRI exposure remained associated with internalizing and anxious behavior scores after controlling for current maternal depression, depression during pregnancy, and multiple other risk factors.

**Discussion:** Results of this study suggest that developmental exposure to maternal depression or anxiety and to the medications used to treat maternal mood disturbances are associated with increased levels of internalizing behaviors and anxiety at school age. However, several limitations of the study should be noted. The relationship between the timing and duration of the SRI exposure and childhood behavioral outcomes could not be examined as the majority of mothers received SRIs through most of their pregnancy. In addition, given that the behavioral outcomes were based on maternal report, the possibility that the relationship between in-utero SRI exposure and childhood behavior is a result of maternal depression cannot be ruled out. Finally, maternal genetics were not evaluated and it is possible that exposed infants were genetically predisposed toward internalizing behaviors and anxiety.

Hanley G, Brain U, Oberlander T: Prenatal exposure to serotonin reuptake inhibitor antidepressants and childhood behaviors. *Pediatric Research* doi 10.1038/pr.2015.77. From the University of British Columbia (UBC), Vancouver, Canada. **Funded by the Child and Family Research Institute (UBC); and the Canadian Institutes of Health Research.** The authors declared no conflicts of interest.

### Transdermal Methylphenidate Skin Changes

According to a warning issued by the FDA, permanent loss of skin color can occur with use of the methylphenidate transdermal system (*Daytrana*).

The skin condition, known as chemical leukoderma, is not physically harmful but is disfiguring. In addition, the condition is not reversible, which can cause patients' emotional distress. The lightened skin sites associated with the methylphenidate patch were reportedly as large as 8 inches in diameter. *Daytrana* labeling has been updated to reflect the risk.

Patients and caregivers should monitor users for new areas of lightened skin, particularly under where the patch has been applied, and alternate treatments should be considered for patients who experience skin color changes.

*Daytrana Patch (methylphenidate transdermal system): Drug safety communication—Permanent Skin Color Changes. Available at www.fda.gov/safety/medwatch.*
Reference Guide

Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance and large effect sizes do not ensure treatment efficacy.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that one group has half the risk of the other group.

Mortality Ratio: A quantity, expressed as either a ratio or percentage, quantifying the increase or decrease in mortality of a study cohort with respect to the general population.

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 are posted at www.alertpubs.com.

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