Conduct Disorder in Girls

Longitudinal data indicate conduct disorder (CD) and associated problems emerge prior to adolescence in girls. Preventive measures should be targeted to early childhood.

Methods: The Pittsburgh Girls Study (PGS) is a community-based longitudinal evaluation of CD in 2451 young girls recruited at ages 5–8 years. Because low-income is a known risk factor for disruptive behavior disorders, children from that group were oversampled. Annual interviews were conducted separately with the child and her parents to collect information on disruptive behavior disorders; substance use; other psychiatric disorders; temperament; peer relationships; trauma; personal resources; and living environment. Teacher data were also obtained.

Results: In the first study year, the prevalence of oppositional defiant disorder ranged from 3.5 to 5%, and conduct disorder was uncommon. Over time, 510 girls (21%) met DSM-IV criteria for CD at 1 or more evaluation. Nearly all (n=469; 92%) had onset between ages 7 and 9 years; the remaining patients had onset after age 10. Conduct problems were significantly associated with low parental warmth and harsh punishment (p<0.01). In addition, the girls’ conduct problems were predictive of these types of parenting behavior in the subsequent year.

Starting in study year 3, girls were questioned at the annual evaluation about prior year alcohol use. Initially rates of alcohol experimentation were low but higher among African American girls, and they increased with age. In contrast, by the time they reached age 15, 45% of girls of European American descent and 24% of African American girls reported prior year alcohol use. Substudies of the PGS are currently evaluating sexual outcomes and young motherhood as well as precursors to comorbid depression.


Basal Ganglia Morphology and Stimulants in ADHD

Magnetic resonance imaging (MRI) scans showed altered basal ganglia morphology in children with ADHD. The changes were partially attenuated by stimulant medication.

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Methods: Study participants were 47 patients with ADHD and 57 others with no medical, psychiatric, or neurologic illness. All were aged 7–18 years. Volume and surface morphology of the 3 basal ganglia (i.e., caudate, putamen, and globus pallidus) were measured using MRI. Symptom severity was measured at the time of the scan using the Barkley, DuPaul, and McMurray ADHD rating scale.

Results: The patients with ADHD had significantly smaller average putamen volumes than the comparison subjects. Overall caudate and globus pallidus volumes did not differ between the 2 groups. ADHD was associated with marked inward deformations of multiple areas of the putamen surface and with smaller inward deformations of the caudate and globus pallidus.

Among the patients with ADHD, stimulant medication did not affect basal ganglia volume. However, patients using stimulants showed significant outward deformations of the basal ganglia surfaces, while patients who were not using stimulants had exacerbated inward deformation of these surfaces. ADHD symptom severity was correlated with the magnitude of inward deformations of the basal ganglia surface.

Discussion: Previous MRI studies have shown reduced volumes of the cerebral cortex and 1 or more basal ganglia in children with ADHD. The surface analyses of the present study provided a level of detail that showed highly localized anatomical disturbances. Inward deformations were located in the limbic portions of the basal ganglia, consistent with other studies showing abnormalities in limbic structures in persons with ADHD. The limbic portions of the basal ganglia connect and interact with the orbital frontal cortex, amygdala, and nucleus accumbens to form the distributed limbic neural circuit that guides reinforcement-based learning. Abnormalities in this circuit may account for ADHD patients' problems with delayed gratification and selecting appropriate behaviors for a given situation. Other basal ganglia surface abnormalities seen in this study may underlie complex sensorimotor impairment.

Histamine Gene Moderates Food Additive Effects

A histamine gene polymorphism may mediate the effects of artificial food colorings on ADHD symptoms.¹

Background: Genetic factors are believed to be a major contributor to individual differences in ADHD symptoms, but those genes identified have only small effects. Food additives have also been shown to adversely affect behavior in children with ADHD.² ³ Histamine is associated with inhibition learning in experimental animals and may mediate the effects of artificial food colors in the central nervous system.

Methods: Study subjects were a group of 3-year-old children (n=132) and another group of 8- and 9-year-old children (n=119), sampled without regard to behavior. All children underwent a 6-week food challenge study. After a week of their normal diet, they had 1 week of withdrawal of target food color additives and administration of a placebo drink. They then had a week each of challenge with fruit drinks containing the 2 different food coloring mixes and placebo, in randomized order. Each challenge was followed by a 1-week placebo washout. Both mixes contained the preservative sodium benzoate.

Participants were genotyped for 2 different histamine degradation alleles and for other genes previously implicated in ADHD: dopamine transporter, dopamine D4 receptor, cate-

chol 0-methyltransferase, and alpha 2A-adrenergic receptor. Global hyperactivity, the primary outcome measure of the challenge, was assessed in the children using a combination of age-appropriate parent and teacher behavioral rating scales and by direct classroom observation.

**Results:** At baseline, presence of histamine and dopamine D4 receptor polymorphisms was associated with global hyperactivity in the 3-year-olds. None of the genetic polymorphisms were associated with baseline global hyperactivity in the older children.

ADHD behavior was affected in the 3-year-old children during the challenge with 1 of the food additives mixtures, but not the other. The effect was mediated by the 2 histamine gene polymorphisms. Neither of the additive mixtures was affected by polymorphisms in the other genes. In the 8- and 9-year-olds, both mixes interacted with the histamine gene polymorphisms, but not with the other genes beyond the DAT1 polymorphism.

**Discussion:** These observations suggest that the current focus on catecholamines in studies of ADHD needs to be extended to other neurotransmitters. The findings may help to explain why genetic studies to date have accounted for so little of the variance in ADHD risk.

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

1 Stevenson J, Sonuga-Barke E, McCann D, Grimshaw K, et al: The role of histamine degradation gene polymorphisms in moderating the effects of food additives on children’s ADHD symptoms. American Journal of Psychiatry 2010; doi: 10.1176/appi.ajp.2010.09101529. From the University of Southampton, U.K.; and other institutions. Funded by the U.K. Food Standards Agency. Two of the 8 study authors disclosed commercial relationships including speaker and advisory board participation for multiple pharmaceutical industry sources. The remaining authors have no potential conflicts of interest.


*See Reference Guide.

**Treating Depression Reduces Oppositionality**

Successful treatment of depression resulted in a reduction in oppositional symptoms, according to a secondary analysis of a controlled treatment trial.1 Treatments that included a medication component had large effects.

**Methods:** The TADS (Treatment for Adolescents with Depression Study) compared 12 weeks of treatment with fluoxetine (Prozac), CBT, combined therapy, or placebo in 439 clinically depressed adolescents. Patients were aged 12–17 years and met DSM-IV criteria for major depressive disorder. Thirteen percent of patients who enrolled in TADS had a diagnosis of oppositional defiant disorder. The presence of a severe conduct disorder was a criterion for exclusion. Oppositionality was assessed with the Conners Parent Rating Scale-Revised (CPRS-R).

**Results:** Primary TADS results showed that all active treatments were effective for depression.2 A comorbid disruptive behavior diagnosis was not predictive of clinical response or premature withdrawal from treatment.

At baseline, patients had a median CPRS-R oppositionality score of 16. Scores decreased significantly by week 12 in all groups, to a mean of about 12 with CBT or placebo and to about 9 with fluoxetine monotherapy and 8 with combination therapy. These changes represent a decrease from clinical to subclinical levels. Regimens that included pharmacotherapy were significantly more effective than those that did not (p<0.01).
Reductions in depression severity accounted for 25% of the reduction in oppositional symptoms. When the analysis was limited to patients whose depression remitted, all 3 active treatments were associated with marked decreases in oppositionality. These were statistically superior to placebo (p<0.01) for the medication regimens. Among patients whose depression did not remit, medication regimens remained more effective and CBT still did not differ from placebo.

Discussion: These results suggest treating depression, particularly with fluoxetine, may be helpful in controlling oppositional behavior. However, the risk of suicidality in adolescents with depression receiving SSRI therapy must be considered.

1 Jacobs R, Becker-Weidman E, Reinecke M, Jordan N, et al: Treating depression and oppositional behavior in adolescents. *Journal of Clinical Child & Adolescent Psychology* 2010; 39(4):559–567. From Northwestern University Feinberg School of Medicine, Chicago, Ill.; and other institutions. **Funded by the NIMH. Two of the 7 study authors disclosed commercial relationships with pharmaceutical industry sources.**


### Migraine and Psychopathology

A literature search identified 7 studies describing psychological function and/or psychiatric comorbidity in 268 clinically treated young patients (≤18 years; mean age, 12 years) with migraine. Strong evidence from these studies suggests children with migraine do not exhibit more withdrawn, delinquent, or aggressive behavior and do not have more thought or social problems than healthy children. There is, however, strong evidence of increased somatic complaints and internalizing behavior, although these are likely a consequence of the disease rather than a sign of psychological dysfunction. Limited evidence suggests that children with migraine are more likely to have a diagnosis of oppositional defiant disorder, but not ADHD, conduct disorder, or dysthymia. Evidence regarding anxiety, depression, attention problems, and externalizing behavior in children with migraine was inconclusive. Study quality was assessed but because 26 different outcome measures were used, a meta-analysis could not be performed. Instead a best-evidence synthesis* approach, in which evidence is graded based on the strength and consistency of study results, was used.

Bruijn J, Locher H, Passchier J, Dijkstra N, et al: Psychopathology in children and adolescents with migraine in clinical studies: a systematic review. *Pediatrics* 2010;126:323–332. From Vlietland Hospital, the Netherlands; and other institutions. **Funded by the Nolet Foundation; and Van der Linden Struciton. The authors disclosed they have no commercial relationships relevant to this article.**

*See Reference Guide.

### Lithium Pharmacokinetics

Although a mainstay in the treatment of adult bipolar disorder, lithium has received little study in young patients. As a result, the FDA called for rigorous research on its use in children and adolescents. The Collaborative Lithium Trials (CoLT) aims to characterize the pharmacokinetics and biodisposition of lithium, establish evidence-based dosing strategies, and examine short and long-term efficacy and safety in pediatric bipolar disorder. The initial CoLT report characterizes lithium pharmacokinetics in 39 patients with bipolar I disorder (manic or mixed state) currently enrolled in a dose-escalation study.

**Methods:** Twenty of the patients were aged 7–11 years, and the remaining 19 were aged ≥12 years; mean age was 11.8 years. Participants received a single randomly assigned lithium dose of 600 or 900 mg. The planned dose for subjects weighing <20 kg was 300 mg, but no subject was small enough to receive this dose. Lithium levels and pharmacokinetic parameters were evaluated over 24 hours. All patients then went on to receive 8 weeks of escalating-dose treatment.
Results: Plasma lithium concentrations were highly variable among subjects. The average half-life was 2.4 hours, significantly shorter than that reported in adults. Clearance and volume of distribution were correlated with body weight, height, body mass index, and fat-free mass.* Pharmacokinetics were unrelated to age, race, gender, or sexual maturation state; however, the sample size may have been too small to detect any effects.

Discussion: These results suggest that lithium’s pharmacokinetic differences between children and adults may be primarily based on body weight and composition. The authors recommend initial dose selection based on fat free mass followed by therapeutic monitoring to ensure safe, effective treatment.

Findling R, Landersdorfer C, Kafantaris V, Pavuluri M, et al. First-dose pharmacokinetics of lithium carbonate in children and adolescents. *Journal of Clinical Psychopharmacology* 2010; doi 10.1097/JCP.0b013e3181e66a62. From the University Hospitals Case Medical Center and Case Western Reserve University, Cleveland, Ohio; and other institutions. Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development; and the NIH. Several study authors disclosed commercial relationships that might pose potential conflicts of interest.

*See Reference Guide.

How Do Your Colleagues Treat Pediatric Insomnia?

A 2009 article in the *Journal of the American Academy of Child and Adolescent Psychiatry* reviewed pharmacotherapeutic options for pediatric insomnia.¹ Antihistamines, melatonin, and several herbal preparations were judged to have relatively strong evidence of efficacy, but no medication is FDA approved to treat insomnia in patients under age 18 years. A national survey of child psychiatrists has now been conducted to examine clinical patterns in the use of pharmacotherapy for pediatric insomnia.²

**Methods:** Surveys were mailed to 6091 members of the American Academy of Child and Adolescent Psychiatry. The questionnaire was completed anonymously and included information on the prevalence of insomnia in the respondent’s practice; medication strategies to manage insomnia and the frequency of their use in a range of psychiatric disorders; and reasons for and against prescribing medication. Both prescription and over-the-counter medications were considered. The survey also collected information on the respondent’s training, practice type, and other demographic information.

**Results:** After 2 survey mailings, 1273 questionnaires were returned and deemed eligible for evaluation. Overall, psychiatrists reported that 29% of their patients considered insomnia a major problem. The prevalence ranged from 8% to 32% and increased with patient age. Nearly 17% of pre-schoolers and 25% of elementary school-aged children were treated with medication. Over-the-counter antihistamines were recommended by 81% of psychiatrists, and melatonin by 51%. See table for rates with common prescription medications.

Alpha agonists were prescribed significantly more often for ADHD (81% of physicians) than for mood or anxiety disorders or mental retardation (31%–67%). Trazodone was used most frequently in patients with mood and anxiety disorders (78% and 72%, respectively). Atypical antipsychotics, anticonvulsants, and short-acting hypnotics were also likely to be prescribed for patients with mood disorders.

<table>
<thead>
<tr>
<th>Medications for Insomnia Prescribed by Psychiatrists</th>
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<tr>
<td>Alpha agonists</td>
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<tr>
<td>Trazodone</td>
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<tr>
<td>Sedating antidepressants</td>
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<td>Atypical antipsychotics</td>
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<td>SSRIs</td>
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<td>Benzodiazepines</td>
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<td>Short-acting hypnotics</td>
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Concerns about daytime "hang-over" effects (81%) and side effects (67%) were the most common reasons cited for not prescribing medication for insomnia. Potential for abuse and suicide were also common concerns.

**Discussion:** These results suggest child psychiatrists are comfortable prescribing a wide variety of medications for their patients with sleep disturbances, particularly those with primary insomnia or severe mood or anxiety disorders such as bipolar disorder and PTSD. However, evidence is sparse, and well designed controlled studies of hypnotic medications are needed to establish effective dosing ranges and relative safety and efficacy.


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**Reference Guide**

**Best-Evidence Synthesis:** Divides scientific evidence into 4 levels based on strength and reproducibility of results. Grade 1 is strong evidence: more than 1 relevant high-quality study with generally consistent outcomes. Grade 2 is moderate evidence: 1 relevant high-quality study and ≥1 lower-quality study with generally consistent outcomes. Grade 3 is limited evidence: 1 relevant high-quality study or >1 relevant but low-quality studies with generally consistent outcomes. Grade 4 is inconclusive evidence: 1 relevant low-quality study, no relevant studies, or inconsistent outcomes.

**Fat-Free Mass Index (FFMI):** Similar to the body mass index (BMI), but the FFMI takes into account the amount of muscle mass and relates that to height. It is not necessarily superior to BMI, but it does factor in different parameters than simply total weight.

**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.