Evidence from a neuroimaging study suggests that severe mood dysregulation (SMD) is not a developmental presentation of bipolar disorder.

**Background:** One controversial aspect of the diagnosis of pediatric bipolar disorder is whether it includes children with nonepisodic severe irritability (SMD) and symptoms of hyperarousal, similar to those seen in children with ADHD. Results of familial and longitudinal studies suggest SMD is not a developmental presentation of bipolar disorder, but additional evidence from neuroimaging studies would help resolve the question. Children with SMD are believed to have impaired motor inhibition. The present study (part of an ongoing NIH study of bipolar disorder) was conducted to determine whether behavioral disinhibition in the 2 disorders, despite their clinical similarity, have different neural mechanisms.

**Methods:** Motor inhibition was studied using the stop signal task in youths aged 8–18 years: 32 with bipolar disorder, 26 with SMD, 17 with ADHD, and 21 healthy controls. Scans were obtained during a task requiring subjects to respond correctly to a presented signal unless a "stop" signal appeared, at which point they would have to inhibit their response. The study participants with ADHD but no mood disorder were a second control group included in order to determine whether differences in inhibition in bipolar disorder could be attributed to comorbid ADHD.

**Results:** The groups did not differ on the 3 tests of correct "go" responses or successful inhibition included in the analysis. On tests of failed inhibition, between-group differences were observed in the right anterior cingulate cortex and right nucleus accumbens, areas known to be involved in motor inhibition. Neural activation in these areas was significantly less in youths with bipolar disorder than in the group with SMD and healthy controls, who did not differ from each other. Youths with bipolar disorder differed from those with ADHD in some findings, but participants with bipolar disorder without ADHD did not differ from participants with ADHD and no mood disorder. Study results were not affected by patients' present mood state or stimulant medication.
**Discussion:** Little is known about the pathophysiology of SMD, although it is as impairing clinically as bipolar disorder. The lack of difference between children with SMD and healthy controls in this study is surprising given that most of the patients with SMD also met criteria for ADHD. Possibly the pathophysiology of ADHD differs when it occurs in the setting of a mood disorder, representing a unique interaction between mood and attention problems. Limbic circuitry, rather than prefrontal circuitry, may be more involved in inhibition in both bipolar disorder and SMD.


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**Possible Blood Test for ADHD**

A preliminary manufacturer-sponsored study suggests that a blood test could potentially be helpful in diagnosing ADHD. The test measures the membrane potential of blood cells relative to a buffer, resulting in the membrane potential ratio (MPR). An earlier study found that patients with bipolar disorder had decreased MPRs compared with control subjects. The results of that earlier study suggested the MPR may also distinguish patients with ADHD from others.

Study participants were patients from private clinical psychiatry practices. They included 148 children, adolescents, and adults with ADHD; 59 patients with bipolar disorder; and 169 persons with neither disorder. No study patients had comorbid ADHD and bipolar disorder. Clinical diagnoses were assigned following DSM-IV criteria and were used for ratings of the test's sensitivity and specificity. The World Health Organization’s Adult Self-Report Scale (ASRS) was also used in patients with ADHD.

According to MPR test values, patients with bipolar disorder were relatively hyperpolarized while those with ADHD were relatively depolarized compared with controls. Values in the 3 groups differed significantly from one another. The sensitivity of the MPR for ADHD (i.e., its ability to correctly identify persons with the disorder) was 0.9 compared with the ASRS and 0.75 compared with DSM-IV-based clinical diagnosis. The specificity of the test (i.e., its ability to distinguish ADHD from non-ADHD) was 0.75.

**Clinical Implications:** An objective laboratory test for ADHD would be helpful because the disorder appears to be often inappropriately diagnosed, and comorbid disorders can further complicate diagnosis. This is a pilot study that requires much additional confirmation, including comparison with a true gold standard and testing in patients free of medication, which can alter the membrane potential of blood cells. The MPR, while not as accurate in ADHD as in bipolar disorder, still compares favorably with some other tests for complex diseases.

Woodruff D, El-Mallakh R, Thiruvengadam A: A potential diagnostic blood test for attention deficit hyperactivity disorder. Attention Deficit Hyperactivity Disorder 2011;3:265–269. From PsychNostics, LLC, Baltimore, Md.; and the University of Louisville School of Medicine, Louisville, Ky. Funded by PsychNostics, developers of the MPR test. Two of the study authors disclosed financial relationships with commercial sources including PsychNostics.

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**Intervening in Children of Mentally Ill Parents**

According to a meta-analysis, interventions to prevent mental health problems in children of mentally ill parents are generally effective.

**Methods:** A literature search identified 13 clinical trials published before mid-2010 that evaluated preventive interventions for children of parents with mental illness and met quality criteria for randomized controlled trials. Child outcomes included development of the same mental disorder as the parent, and internalizing and externalizing symptoms.
**Results:** The trials enrolled a total of 1490 children (range, 30–316 per study) and 1404 parents, most of whom were mothers. Parental depression was addressed in 7 studies, affective disorders in 2, anxiety disorders in 1, and drug or alcohol dependence in 3. The most common therapeutic interventions to increase parenting skills were cognitive or behavioral therapy and psychoeducation. Two programs aimed to increase resilience in adolescents using psychoeducation. In 4 studies, the intervention was delivered to the family, and in the rest it was limited to 1 or both parents.

Six studies, with follow-ups ranging from 6 months to 15 years, examined the incidence of the same mental disorder as the parent in the child. Incidence was decreased by 40% in children of families that received the intervention compared with controls (p<0.001). The number needed to treat* in order to prevent 1 incident mental disorder in the children was 17.

Seven studies examined the effect of treatment on internalizing and externalizing symptom severity in the children. Both were reduced, but the effects were small and, in the case of externalizing symptoms, not statistically significant. There was no strong evidence that interventions involving parents and children were better at reducing these symptoms than parent-only interventions.

**Discussion:** The results of this analysis can be generalized to mothers with affective disorders, but not to other populations. In spite of this and other study limitations, the results argue for more rigorous investigation of interventions to prevent mental illness in children of mentally ill parents.

**Study Rating*—16 (89%):** This study met most criteria for a meta-analysis, but the source of funding was not stated.

Siegenthaler E, Munder T, Egger M: Effect of preventive interventions in mentally ill parents on the mental health of the offspring: systematic review and meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry* 2012;51 (January):8–17. From the University Psychiatry Hospital, Bern, Switzerland; and other institutions. Source of funding not stated. The authors disclosed no competing interests.

*See Reference Guide.

### New Guideline for Pediatric OCD

A new practice parameter for assessing and treating obsessive-compulsive disorder in children and adolescents has been published by the American Academy of Child and Adolescent Psychiatry. The parameter represents a significant update from the previous 1998 guideline, as new knowledge has been gained from genetic and phenotypic studies, clinical trials of pharmacologic and nonpharmacologic treatment, and emerging data on predictors of response to specific therapies.

About 1–2% of U.S. children have a diagnosis of OCD. Preadolescence is 1 of the 2 lifetime peaks of incidence (with the other being early adulthood). While genetic influences have been identified, many or most cases are sporadic, arising without a known family history. The highly controversial syndrome of pediatric autoimmune neuropsychiatric disorder (PANDAS) may reflect only 1 of many nonspecific immunologic or other physiologic factors (in this case, group A beta-hemolytic streptococcus) that can trigger an increase in OCD symptoms. The prognosis of pediatric OCD is better than previously believed; in many children, OCD remits entirely or becomes subclinical over time. However, patients who have had pediatric OCD have high levels of other problems with peer relationships and employment, although their educational achievement does not appear to differ from that of their peers.

The practice parameter recommends that child and adolescent psychiatrists screen for OCD in all children, regardless of presenting complaint, and that children with suggestive symptoms
be fully evaluated with the DSM-IV-TR criteria and a scalar instrument such as the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), currently the standard rating scale. A complete psychiatric evaluation should be performed, given the high prevalence of comorbid disorders associated with OCD. Medical, developmental, family, and school histories should also be included.

Cognitive-behavioral therapy (CBT) is recommended as first-line treatment for mild-to-moderate OCD when possible; however, a recent survey found the technique to be underutilized in pediatric OCD. CBT plus medication is recommended for patients with moderate-to-severe symptoms and for those in whom CBT has failed to produce adequate improvement. Psychiatric comorbidity should be considered when selecting an initial treatment; for example, children with tics are more likely to respond to CBT, alone or with medication, while those with first-degree relatives with OCD are less likely to respond to CBT. Children with fewer comorbid externalizing symptoms and better insight are also better candidates for CBT.

SSRIs are considered first-line medications, with clomipramine (Anafranil) as a highly effective option. Complete evaluation of medical and cardiac status is required before starting clomipramine. The medications are generally safe and well tolerated in children but should be dosed conservatively, with modest increases no more often than every 3 weeks. It may take as long as 12 weeks for the medication to produce substantial benefits. Pharmacotherapy after stabilization should be continued for 6–12 months and then withdrawn very gradually. Adverse effects, including behavioral activation, are sensitive to dose adjustment, but a switch to an alternate drug is indicated if decreasing the dose does not improve behavioral activation. Medication augmentation is only indicated for children whose OCD is nonresponsive to either CBT plus ≥2 SSRI trials or to 1 SSRI and 1 clomipramine trial. Partial response is more common than nonresponse and should lead to augmentation only if monotherapy has been explored fully (with sufficient doses and duration of treatment) and there is moderate persisting impairment in ≥1 important functional domain.


Late Adolescence: Natural History of Self-Harm

Most adolescent self-harm resolves during the transition to young adulthood, according to results of a longitudinal study.

Methods: Study participants were Australian youths, aged 14–15 years when first surveyed. Participants were interviewed at 6-month intervals until age 19 years and then every few years until ages 28–29 years, for a total of 9 waves. In each wave, respondents were asked a screening question about self-harm, and those who responded positively were asked to describe each episode. Symptoms of depression and anxiety were also assessed with clinical interviews.

Results: A total of 1900 individuals responded to the self-harm question in ≥1 wave of interviews, and 1652 responded at least once in both the adolescent and young-adult phases. Ninety percent did not report any self-harm during any life phase. About 8% reported self-harm as adolescents—6% of males and 10% of females. Self-harm was carried out with suicidal intent in slightly less than 1% of adolescents. About 2.5% of participants reported deliberate self-harm in their 20s, with proportions similar in young men (1.9%) and women (3.2%).

Sharp declines in rates of self-harm occurred during the late adolescent years, so that by age 17 years, rates were markedly reduced from mid-adolescence. Cutting and burning were the most

A single male subject reported self-harm during both adolescence and young adulthood. However, in females, self-harm in adolescence was associated with a ≥5-fold greater risk of self-harm in young adulthood.

After adjusting for multiple demographic factors, self-harm in adolescents was associated with a mixed depression–anxiety state, cannabis use, antisocial behavior, cigarette smoking, and high-risk alcohol use, indicating that many young people who self-harm have other emotional problems that might not resolve without treatment. These associated disorders should be an important focus of early intervention. Mixed depression–anxiety in adolescence was the sole factor clearly associated with self-harm into adulthood; adolescent high-risk alcohol use and cigarette smoking showed no such association.


Adjunctive Guanfacine in ADHD

In a manufacturer-sponsored, multicenter controlled trial, extended-release guanfacine was effective as adjunctive treatment for children and adolescents with ADHD who had experienced suboptimal responses to stimulants.

Methods: Study subjects (n=455), aged 6–17 years, had mild-to-moderate residual ADHD symptoms despite ≥4 weeks of extended-release mixed amphetamines, lisdexamfetamine, or methylphenidate. Patients received 9 weeks of double-blind adjunctive treatment with guanfacine (either morning or evening) or placebo. Dosage of the study medication was optimized to a maximum of 4 mg/day in the first 5 weeks, held stable at the optimal dosage for 3 weeks of maintenance, and then tapered over 9 days. The primary efficacy measure was change from baseline in the 18-item ADHD Rating Scale-IV, with a 4-point decrease indicating clinically meaningful improvement.

Results: A total of 386 patients completed at least the maintenance phase, and patients in all treatment groups took >95% of their study medication. The mean optimal guanfacine dosage was 3.2 mg/day (weight-adjusted range, 0.05–0.12 mg/kg). Patients who received guanfacine had significantly greater improvement in ADHD symptoms than those who received placebo. Both hyperactivity/impulsivity and inattention improved to a similar degree. Average scores, relative to changes in the placebo group, decreased by 4.5 points with guanfacine morning dosing and 5.3 points with evening dosing. The effect sizes* for these outcomes were in the range of about 0.35–0.45. Clinical Global Impression-Severity scores reflected similar improvements in the morning- and evening-dose guanfacine groups.

<table>
<thead>
<tr>
<th></th>
<th>Baseline Total ADHD-RS-IV</th>
<th>Endpoint Total ADHD-RS-IV</th>
<th>Effect Size</th>
<th>% of Patients Improved</th>
<th>% of Patients Mildly Ill or Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guanfacine AM</td>
<td>37.6</td>
<td>17.3</td>
<td>0.38</td>
<td>71%</td>
<td>76%</td>
</tr>
<tr>
<td>Guanfacine PM</td>
<td>37.0</td>
<td>16.1</td>
<td>0.45</td>
<td>74%</td>
<td>76%</td>
</tr>
<tr>
<td>Placebo</td>
<td>37.7</td>
<td>21.7</td>
<td>-----</td>
<td>58%</td>
<td>61%</td>
</tr>
</tbody>
</table>
Treatment-emergent adverse events occurred in about 77% of guanfacine-treated patients and in 63% of the placebo group. Rates of serious adverse effects and discontinuation because of them were somewhat higher in the 2 guanfacine groups (about 2–6%) than in the placebo group (<1%). Treatment-emergent somnolence, sedation, and hypersomnia affected about 18% of guanfacine-treated patients, compared with 6% of those receiving placebo. Guanfacine-treated patients had small decreases in blood pressure and pulse rate. Most adverse effects occurred during the first 5 weeks of treatment and were mild to moderate.

Discussion: Guanfacine is currently FDA-approved as both monotherapy and adjunctive treatment for ADHD, but there has been little previous published clinical research of its adjunctive use. It has been suggested that guanfacine may oppose some of the adverse effects of stimulants on blood pressure, pulse, and weight. The present study showed only small effects on these measures. In contrast to older case reports of adverse cardiovascular effects with adjunctive use of other alpha-2 agonists, the present study raised no concerns about cardiovascular toxicity.

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


Drug Trade Names: guanfacine, extended release—Intuniv; lisdexamfetamine dimesylate—Vyvanse; methylphenidate, extended-release—Concerta, Focalin, Metadate, Ritalin; mixed amphetamine salts—Adderall

*See Reference Guide.

Reference Guide

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.

Number Needed to Treat (NNT): Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value the less effective is the treatment.

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.