Severe Mood Dysregulation or Bipolar Disorder?

The diagnostic boundaries between severe mood dysregulation and bipolar disorder are controversial. The marked increase in diagnosis of pediatric bipolar disorder since the 1990s results in part from a change in how the disorder is conceptualized. Some researchers believe that mania presents differently in youths than adults—as persistent, nonepisodic, severe irritability. A review of all articles on pediatric bipolar disorder or irritability, published in major psychiatric journals over the past 20 years, suggests important differences between the 2 syndromes.¹

Researchers at the NIMH defined a syndrome called "severe mood dysregulation" that defines irritability as frequent, extreme, and developmentally inappropriate temper outbursts, with negative mood (anger or sadness) between these outbursts. Irritability symptoms must be severely impairing, present for at least 1 year, and not associated with psychosis, mania, or hypomania. A total of 146 youths meeting criteria for severe mood dysregulation have been studied at the NIMH in recent years. These patients are as severely impaired as those with a diagnosis of bipolar disorder, and about 60% had a community diagnosis of bipolar disorder at the time of study entry. There is also marked diagnostic overlap with oppositional defiant disorder and ADHD, and somewhat less overlap with anxiety and depressive disorders.

Results of longitudinal studies indicate that over 2 years most of these youths do not go on to have manic episodes. Retrospective analyses of community samples of affected youths followed for up to 20 years also show a low likelihood of bipolar disorder in adulthood. Adolescent irritability does, however, appear to predict adult anxiety and depressive disorders. Family studies, although few, suggest severe irritability is not strikingly associated with bipolar disorder in relatives.

Researchers have attempted to identify neural mechanisms that act as biomarkers for the specific syndromes. Young patients with bipolar disorder and those with severe mood dysregulation have in common deficits in facial emotion labeling, frustration tolerance, and sensitivity of behavior to context. However, results of neuroimaging studies indicate the mediating neural circuitry underlying these deficits differs in the 2 groups.
There has been only 1 treatment study of severe mood dysregulation—a negative trial of lithium. However, a study of SSRI treatment is now underway. Clinicians may be reluctant to prescribe SSRIs or stimulants in this patient population for fear of inducing mania, but preliminary data indicate these patients may respond well to stimulants.

The existing research on severe mood dysregulation points to the conclusion that the diagnosis of mania should be more strictly applied only to patients with the classic symptoms. However, severe mood dysregulation is as impairing as pediatric bipolar disorder and far more common. Treatment studies are urgently needed.

**Editor’s Note:** In response to the increase in pediatric bipolar disorder and the debate about its diagnosis in young patients, a new diagnostic category, temper dysregulation disorder with dysphoria (TDD), has been proposed for the 2013 release of the DSM-V diagnostic manual. The proposed criteria for TDD are nearly identical to those proposed for severe mood dysregulation. Regardless of the name, the new category is controversial and could profoundly affect how some young patients are treated. Supporters of the TDD category believe its adoption in DSM-V will drive much needed research on severe irritability.

**Methylphenidate-Associated Priapism**

Priapism is a persistent, painful erection that is not associated with sexual stimulation or desire; it can lead to permanent erectile dysfunction. Many drugs reportedly cause the reaction, but it is uncommon in young patients taking psychotropic medications. The present case appears to be the first associated with immediate-release methylphenidate in an adolescent.

A 14-year-old male with ADHD was treated for 2 months with 10 mg/day immediate-release methylphenidate. Three days after the dosage was increased to 20 mg/day, he began to experience intermittent episodes of priapism 3–4 times/day. Each episode lasted about 40–45 minutes, but they were not painful. The patient was embarrassed by the episodes and did not mention them to his caregivers or doctor. His mother became aware of the priapism about 2 months after onset of the episodes. After physical examination uncovered no medical or other pharmacologic causes, the reaction was suspected to be related to methylphenidate. Treatment was stopped, and the priapism resolved after 3 days. The reaction did not recur with subsequent sustained-release methylphenidate treatment.

A previous case reported stuttering priapism associated with OROS methylphenidate withdrawal during a drug holiday. The authors suggest the daily occurrence in the present patient was also related to methylphenidate withdrawal, as the half-life of the immediate-release formulation is only 2–3 hours. Although the exact mechanism is unclear, withdrawal of immediate-release methylphenidate may deplete norepinephrine in adrenergic nerves and lead to impaired penile detumescence mechanisms and priapism. The consequences of priapism can be irreversible, and because adolescents may be reluctant to spontaneously report its occurrence, the possibility should be discussed with patients and their caregivers.


**Drug Trade Names:** methylphenidate, immediate release—*Ritalin*; methylphenidate, OROS—*Concerta*
Aripiprazole Augmentation for Resistant OCD

Adding aripiprazole to SSRI therapy significantly improved symptoms of obsessive-compulsive disorder in a group of severely impaired adolescents.

**Background:** Cognitive behavioral therapy (CBT) is first-line treatment for OCD in young patients. However, many patients require pharmacotherapy because of insufficient CBT response. Results of meta-analyses have shown that symptoms also remain unresponsive to SSRIs in a substantial portion of these patients. Some atypical antipsychotics can worsen OCD symptoms; however, because aripiprazole is a partial 5-HT1A receptor agonist, it has been proposed as an option for OCD. After a small case series in adults suggested it may be effective in SSRI-resistant OCD, the agent was investigated in a group of adolescents.

**Methods:** Study subjects were referred to a tertiary-care anxiety and mood disorders clinic for evaluation of OCD. Of the 337 referred patients, 57 (17%) responded to psychotherapy and were excluded. A total of 280 patients received clomipramine; fluoxetine; paroxetine; sertraline; or fluvoxamine. The 39 patients, aged 12–18 years (mean age, 15 years), with continued symptoms despite 2 antidepressant trials went on to receive aripiprazole augmentation for up to 6 months. All patients were severely impaired, with a mean Clinical Global Impression (CGI) Severity* score of 6.9 and a mean Children’s Global Assessment Scale (CGAS)* score of 39. Aripiprazole dosages ranged from 5 to 20 mg/day (mean, 12 mg/day). Comorbid bipolar disorder, which was treated with a mood stabilizer, was present in 7 patients, and 3 patients with ADHD also received methylphenidate. Sixteen patients had a comorbid tic disorder or Tourette’s syndrome.

**Results:** At 6-month follow-up, the mean CGI-S score was significantly decreased to 3.5 (p<0.0001), and the mean CGAS score was significantly increased to 49 (p<0.0001). Patients were considered responders if they had 3 consecutive monthly ratings of ≤3 on the CGI-Severity scale, 1 or 2 on the CGI-Improvement* scale, and ≥50 on the CGAS. A total of 23 patients (59%) met response criteria. Neither predominant OCD symptom type (e.g., aggressive, sexual, religious obsessions or compulsions; hoarding) nor comorbid disorders appeared to affect OCD response. Response patterns also did not differ in patients receiving concomitant medications for bipolar disorder, ADHD, or tic disorders. Tics improved with augmentation in 10 of the 16 patients (63%) experiencing them at baseline. A greater degree of baseline functional impairment appeared to be the only predictor of poor response.

Aripiprazole was well tolerated. Mild-to-moderate agitation affected 4 patients (10%), mainly during the first 2 weeks of augmentation. Mild sedation occurred in 4 patients (10%), and 3 patients (8%) experienced sleep disturbances. Mild transitory tremors developed in 1 patient, but they did not require additional medication.

**Discussion:** These results may not generalize to all patient populations, and the conclusions are further limited by the naturalistic study design. Study participants were severely ill, most (71%) were male, and all were Caucasian. However, the positive effects, coupled with the tolerability of aripiprazole, suggest additional research may be warranted.


**Drug Trade Names:** aripiprazole—Abilify; clomipramine—Anafranil; fluoxetine—Prozac; fluvoxamine—Luvox; paroxetine—Paxil; sertraline—Zoloft

*See Reference Guide.*
**Reference Guide**

**Children’s Global Assessment Scale (CGAS):** A rating of overall psychopathology. Scores can range from 1 to 100, and treatment is considered necessary if a patient’s score is ≤60. A score of 50 indicates moderate impairment that is easily observable in most situations.

**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.

**Clinical Global Impression Severity (CGI-S) Scale:** A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

**CHILD & ADOLESCENT PSYCHIATRY ALERTS, VOLUME XII, 2010 INDEX**

<table>
<thead>
<tr>
<th>Issue Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pages.................................Month</td>
</tr>
<tr>
<td>1–6.................................January</td>
</tr>
<tr>
<td>7–12.................................February</td>
</tr>
<tr>
<td>13–18.................................March</td>
</tr>
<tr>
<td>19–24.................................April</td>
</tr>
<tr>
<td>25–30.................................May</td>
</tr>
<tr>
<td>31–36.................................June</td>
</tr>
<tr>
<td>37–42.................................July</td>
</tr>
<tr>
<td>43–48.................................August</td>
</tr>
<tr>
<td>49–54.................................September</td>
</tr>
<tr>
<td>55–60.................................October</td>
</tr>
<tr>
<td>61–66.................................November</td>
</tr>
<tr>
<td>67–72.................................December</td>
</tr>
</tbody>
</table>

**A**

**ADHD**
- Atomoxetine Extended Treatment, 11
- Atomoxetine Response Predictors, 50
- Aggression Treatment, 43, 49
- Basal Ganglia Morphology, 37
- Clonidine with Stimulants, 61
- Cognitive Deficits and Self-Perception, 50
- Comorbid Tics and Methylphenidate, 27
- Conduct Disorder and Substance Abuse, 62
- Depression and Suicide Risk, 61
- Divalproex for Aggression, 2
- Fetal Antidepressant Exposure, 45
- Lisdexamfetamine, 17
- Melatonin for Insomnia, 1
- Pesticide Link, 33
- Prevalence, 10
- School-Entry Delay, 64
- Thalamic Abnormalities, 19
- Understanding Hyperactivity, 19
- Western Diet, 44
- adrenergic agents. See also specific drugs
  - Behavior Disorders, 53
- adverse events
  - Fluvoxamine Disinhibition, 58

**aggression**
- Divalproex in ADHD, 2
- Managing Inpatients, 22
- Treatment in ADHD, 43, 49

**alpha agonists. See also specific drugs**
- Insomnia Treatment, 41

**amphetamine salts**
- Aggression in ADHD, 49

**anticonvulsants**
- Childhood Absence Epilepsy, 16

**antidepressants. See also specific drugs**
- Behavior Disorders, 53
- Fetal Exposure and ADHD, 45
- Insomnia Treatment, 41
- Medication Errors, 17
- Suicide, 26

**antihistamines. See also specific drugs**
- Insomnia Treatment, 41

**antipsychotics**
- Behavior Disorders, 53
- Preschool Use, 14
- Tic Suppression, 51

**antipsychotics, atypical. See also specific drugs**
- Aggression Treatment in ADHD, 43
- Bipolar Disorder Treatment, 14
- Compared, 46
- Insomnia Treatment, 41

**anxiety**
- Methylphenidate for ADHD and Tics, 27
- Prevalence, 10

**aripiprazole**
- Atypical Antipsychotics Compared, 46
- Augmentation in OCD, 69
- Bipolar Disorder Treatment, 14
- Delirium Treatment, 64
- Irritability in Autism, 4

**artificial food coloring**
- ADHD and Histamine Gene, 38

**atomoxetine**
- Extended Treatment, 11
- Metabolism and Low CYP2D6, 44
- Response Predictors, 50
- Tic Suppression, 51

**auditory hallucinations**
- Prevalence in Children, 5

**autism**
- Aripiprazole for Irritability, 4
- Divalproex for Irritability, 3
- Early Start Denver Model, 4

**autism spectrum disorders**
- Differential Diagnosis in OCD, 20

**B**

**basal ganglia morphology**
- ADHD, 37

**behavior disorders. See also specific disorders**
- Pharmacotherapy Trends, 53

**behavior therapy**
- Tourette Disorder, 35

**benzodiazepines. See also specific drugs**
- Insomnia Treatment, 41

**bipolar disorder**
- Antipsychotic Use in Preschoolers, 14
- Atypical Antipsychotic Treatment, 14, 46
- Diagnosing, 8
- DSM-V, 34
- Evidence for Early Markers, 7
- Risperidone vs Divalproex, 55
- Risperidone for Rage, 33
- Severe Mood Dysregulation, 67
- TMS Safety, 29

**botulinum toxin**
- Tic Suppression, 51
bupropion
Antidepressant Errors, 17
Fetal Exposure and ADHD, 45

C, D
catatonia
ECT, Ultra-Brief Pulse, 47
cerebral folate
Deficiency, 27
Child and Family Traumatic Stress Intervention
PTSD, 57
chlorpromazine
Delirium Treatment, 64
“choking game”
Overview, 1
clonidine
Aggression Treatment in ADHD, 43
Approval for Use with Stimulants, 61
Pharmacotherapy for PTSD, 28
Tic Suppression, 51
clozapine
Atypical Antipsychotics Compared, 46
Metformin for Weight Gain, 25
cognitive-behavioral therapy (CBT)
Depression Treatment and Oppositionality, 39
OCD, 52
Pharmacotherapy for PTSD, 28
Resistant Depression, 32
conduct disorder
ADHD and Substance Abuse, 62
Aggression in ADHD, 49
Overview in Girls, 37
Pharmacotherapy Trends, 53
Prevalence, 10
cytochrome P450
Atomoxetine Metabolism, 44
D-cycloserine
OCD, 52
delirium
Overview, 64
depression
ADHD and Suicide Risk, 61
Fatty Acids, 47
Suicide, 26
Treatment Reduces Oppositionality, 39
depression, resistant
Continuation Treatment, 32
Residual Symptoms, 63
TMS Safety, 29
diet, Western
ADHD, 44
diphenhydramine
Inpatient Aggression, 22
disinhibition
Fluvoxamine, 58
disruptive behavior disorders
Antipsychotic Use in Preschoolers, 14
Parent-Child Interaction Therapy, 59
divalproex
Aggression Treatment in ADHD, 2, 43
Bipolar Disorder, 55
Irritability in Autism, 3
donepezil
Tic Suppression, 51
doxepin
Antidepressant Errors, 17
DSM-V
Temper Dysregulation Disorder with Dysphoria (TDD), 34
Tic Disorders, 35
E–F
Early Start Denver Model
Autism, 4
ECT
Ultra-Brief Pulse for Catatonia, 47
epilepsy
Anticonvulsants Comparison, 16
TMS Safety, 29
ethosuximide
Childhood Absence Epilepsy, 16
fatty acids
Depression, 47
Preventing Psychosis, 13
fetal exposure
Antidepressants and ADHD, 45
fluoxetine
Antidepressant Errors, 17
Depression and Residual Symptoms, 63
Depression Treatment and Oppositionality, 39
fluphenazine
Tic Suppression, 51
fluvoxamine
Disinhibition, 58
food additives
ADHD and Histamine Gene, 38
G–K
generalized anxiety disorder
Differential Diagnosis in OCD, 20
genetics
Predicting Suicide, 15
growth effects
Lisdexamfetamine, 17
guanfacine
Pharmacotherapy for PTSD, 28
Tic Suppression, 51
hallucinations
Auditory Vocal in Children, 5
haloperidol
Atypical Antipsychotics Compared, 46
Delirium Treatment, 64
Tic Suppression, 51
histamine gene
ADHD and Food Additives, 38
hypersensitivity
Understanding in ADHD, 19
hypnotics, short-acting. See also individual drugs
Insomnia Treatment, 41
insomnia
Melatonin in ADHD, 1
OROS Metformin, 9
Pharmacotherapy, 41
irritability
Aripiprazole in Autism, 4
Depression and Residual Symptoms, 63
Divalproex in Autism, 3
Nonepisodic in Bipolar Disorder, 34
Severe Mood Dysregulation, 67
L–O
lamotrigine
Childhood Absence Epilepsy, 16
levetiracetam
Tic Suppression, 51
lisdexamfetamine
Growth Effects, 17
lithium
Aggression Treatment in ADHD, 43
Pharmacokinetics, 40
mania
Risperidone vs Divalproex, 55
medication errors
Antidepressants, 17
melatonin
ADHD Insomnia, 1
Insomnia Treatment, 41
metformin
Clozapine Weight Gain, 25
methylphenidate
ADHD and Tics, 27
Aggression in ADHD, 49
Hyperactivity in ADHD, 19
OROS and Sleep, 9
Priapism, 68
migraine
Psychopathology, 40
mood disorders
Prevalence, 10
nefazodone
Pharmacotherapy for PTSD, 28
obsessive-compulsive disorder (OCD)
Aripiprazole Augmentation, 69
D-Cycloserine plus CBT, 52
Differential Diagnosis, 20
Riluzole Safety, 56
olanzapine
Atypical Antipsychotics Compared, 46
Bipolar Disorder Treatment, 14
Delirium Treatment, 64