Stimulants in ADHD with Aggression and Negative Mood

According to an analysis of data from 2 clinical studies, stimulant monotherapy resulted in improvement in aggressive behavior in children with ADHD, a disruptive behavior disorder, and chronically irritable or angry mood. These results argue against the early use of second-generation antipsychotics in these children before stimulant treatment has been optimized.

**Background:** It has become common in recent years for children with disruptive behavior and chronically irritable or angry mood to receive a diagnosis of bipolar disorder. Disruptive mood dysregulation disorder (DMDD), proposed in part as an alternative diagnosis, requires a chronically irritable mood that persists between temper outbursts. This analysis was conducted to compare treatment results in children with and without a persistent negative mood.

**Methods:** Data were collected from 2 clinical trials of adjunctive medication in children with ADHD and a disruptive behavior disorder that was not responsive to primary stimulant treatment. Following a washout of any previous medications, participants (n=156), aged 6–13 years, were entered into the optimization phase of the study. All were started on OROS methylphenidate, with an optional daily dose of shorter-acting methylphenidate. Children whose symptoms did not respond were switched to extended-release amphetamine–dextroamphetamine. In addition, all families received the Community Parent Education program. The trial’s primary outcome, aggression, was measured using the Retrospective–Modified Overt Aggression Scale (R-MOAS), a parent report of the frequency of different types of aggressive behavior. Persistent negative mood was measured using 14 items compiled from other instruments. A factor analysis of the 14 items identified 2 factors: sadness/anhedonia and irritability/low frustration tolerance.

**Results:** Mean time to stimulant optimization was 70 days, and at this point 51% of children met criteria for remission of aggressive behavior, and 13.5% had aggression that was below the studies’ criteria for randomization to adjunctive medication. Nearly one-third of the participants had symptoms that met diagnostic criteria for DMDD at baseline. About three-fourths of
these subjects were frequently angry or easily frustrated. Among the 14 negative mood items, 2 were associated with higher baseline aggression: flat affect and proneness to angry outbursts. None of the individual baseline symptoms was predictive of remission of aggression.

**Discussion:** Results of this study indicate that presence of symptoms consistent with DMDD do not contraindicate stimulant therapy as initial treatment. However, aggression may not improve sufficiently in nearly one-third of children, who may then require augmentation pharmacotherapy and extended behavioral interventions.

Blader J, Pliszka S, Kafantaris V, Sauder C, et al: Prevalence and treatment outcomes of persistent negative mood among children with attention-deficit/hyperactivity disorder and aggressive behavior. *Journal of Child and Adolescent Psychopharmacology* 2016;26 (March):164–173. From the University of Texas Health Science Center at San Antonio; and other institutions. Funded by the NIMH; and other sources including Abbott Laboratories. Five study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.

**Common Drug Trade Names:** methylphenidate—Ritalin; amphetamine–dextroamphetamine—Adderall; OROS methylphenidate—Concerta

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**Pharmacotherapy of Aggression**

Guidelines recommend psychosocial therapies as first-line treatment for aggression in young patients, followed by medications targeted toward the primary underlying disorder. Atypical antipsychotics can be offered after these steps have failed, but polypharmacy should be avoided.

Impulsive aggression is generally reactive, unplanned, and overt. This type of aggression is more common in clinical settings and is more amenable to pharmacological and psychosocial interventions than planned aggression, which is more characteristic of delinquent youth. The most common conditions underlying impulsive aggression are ADHD and disruptive behavior disorders such as conduct disorder or oppositional defiant disorder. Other less common underlying conditions are mood disorders, neurodevelopmental disorders, PTSD, autism spectrum disorders, and intellectual disability.

In young people with ADHD with or without comorbid disruptive behavior disorders, stimulants have been shown to improve aggression. However, they may not adequately control aggression in many patients, and aggression may reappear due to the drugs’ short duration of action. Nonstimulant ADHD medications—atomoxetine and the long-acting α-2 adrenergic agonists clonidine and guanfacine—have more lasting effects on ADHD core symptoms but have not been compared directly to stimulants with regard to aggression, although they are often prescribed for this purpose. Atypical antipsychotics can also be effective when prescribed as adjuncts to ADHD agents, although they do not have FDA approval for this purpose. Mood stabilizers have long been prescribed to control aggression in patients with aggressive conduct disorders.

Behavioral problems and aggression often co-occur with depression and other mood disorders in young patients. Treatment with SSRIs can lead to reduced aggression in children with depression, as long as there is not a longstanding behavioral problem. However, SSRIs and other antidepressants are not recommended for aggression in children or adolescents in the absence of depression. Several studies indicate divalproex reduces aggression in children with bipolar mania; less evidence exists for other anticonvulsants. Lithium is approved for use in adolescents with bipolar disorder, and much anecdotal evidence suggests it is effective for aggression. Several atypical antipsychotics are approved for bipolar disorder in young people; quetiapine and risperidone have particular efficacy against aggression.

For children with autism or intellectual disability, atypical antipsychotics were often prescribed off-label for aggression. Recently risperidone and aripiprazole have demonstrated efficacy in clinical trials and are now FDA approved for this indication. Other, unapproved atypicals
appear to have similar efficacy. Beta-blockers are often prescribed off-label in these children but have not been evaluated in randomized controlled trials. Nonstimulant ADHD medications, such as clonidine and guanfacine, may be effective, particularly if a child has hyperactivity/impulsivity and sleep problems.

Regardless of the underlying or co-occurring conditions, medication for aggression should be used with close patient monitoring. Growth impairment and cardiovascular risk have been extensively debated but do not appear to be major concerns. Obtaining a baseline ECG is suggested only for patients with risk factors. Patients receiving atomoxetine or antidepressants should be monitored for suicide risk. First-generation antipsychotics are associated with extrapyramidal effects, and atypicals may induce weight gain, metabolic syndrome, and hyperprolactinemia.


**Common Drug Trade Names:** aripiprazole—Abilify; atomoxetine—Strattera; clonidine—Catapres; divalproex—Depakene, Depakote; guanfacine—Intuniv, Tenex; quetiapine—Seroquel; risperidone—Risperdal

### Childhood Trauma and Bipolar Disorder

Recent research has clarified the relationship between childhood trauma and bipolar disorder, but guidelines for applying this knowledge in clinical practice are lacking, according to an updated literature review.

Previous reviews of childhood trauma and bipolar disorder were published between 2008 and 2011. The present review, which includes a considerable amount of more recently published research, suggests that each of the 3 subtypes of childhood trauma—emotional, physical, and sexual—is associated with bipolar disorder, although the specific role of each type remains controversial.

The literature shows a consistent association between childhood trauma and several severe clinical characteristics of bipolar disorder: early onset, suicide attempts, and comorbid substance abuse. Associations with other severe characteristics—rapid cycling, psychotic features, and a higher number of lifetime mood episodes—have been shown less consistently. It appears that associations with more severe disease characteristics are driven by strong linkages in girls, with weaker associations in boys. Of the subtypes of trauma, physical and sexual abuse are the most frequently studied, but some research suggests emotional abuse and neglect may be specific risk factors for bipolar disorder.

In patients with bipolar disorder, childhood trauma is linked with increased emotional lability, increased aggression, and cognitive impairment. These deficits may increase vulnerability to other stressors such as cannabis exposure or life events in adulthood. Biological mechanisms, such as neuroplasticity, sleep deficits, and hypothalamic-pituitary-adrenal (HPA) axis function, further complicate the picture.

Childhood trauma should be investigated in all children with established or suspected bipolar disorder because it signals increased risk of a more severe illness over time. Assessment is especially indicated in patients with early-disease onset; suicide attempts; substance abuse; a high number of mood recurrences; or rapid cycling or other manifestations of mood instability. Numerous structured questionnaires have been developed for this purpose. While no particular assessment is recommended over any of the others, the Childhood Trauma Questionnaire is widely used in research and explores many types of trauma.
Evidence-based recommendations for managing trauma in children with bipolar disorder do not yet exist. However, trauma can be addressed with early intervention approaches such as coping strategies, body awareness/mindfulness techniques, and stress management. Studies in patients with established bipolar disorder are sparse, but do include some evidence in favor of eye movement desensitization and reprocessing and of cognitive behavioral therapy for sexually abused children. Therapies that specifically target emotional regulation or cognitive functioning might help counterbalance the effects of trauma.

Aas M, Henry C, Andreassen O, Bellivier F, et al: The role of childhood trauma in bipolar disorders. *International Journal of Bipolar Disorders* 2016; doi 10.1186/s40345-015-0042-0. From the University of Oslo, Norway; and other institutions. Funded by Institut national de la santé et de la recherche médicale (INSERM); and other sources. The authors declared no competing interests.

**Brief CBT for Adolescent Depression**

Treatment with brief cognitive behavioral therapy had small-to-moderate benefits in a group of adolescents with depression who declined antidepressant medication.

**Methods:** The investigators used an HMO’s electronic medical records to identify primary-care patients, aged 12–18 years, who received a diagnosis of major depression and were given a prescription for an antidepressant but either did not fill the prescription or did not refill after the first 30 days. The study excluded patients with bipolar disorder, psychosis, mental retardation, or autism but included those with any other psychiatric comorbidity. Patients were randomly assigned to self-selected treatment as usual (TAU), with or without CBT. The CBT protocol consisted of 2 units, each with 4 individual sessions. The units covered cognitive therapy to address unrealistic thinking and behavioral activation to increase pleasant activities. The units could be completed in either order, and patients who recovered after a single unit were not required to complete the second. Up to 6 elective continuation contacts were permitted. Patients were assessed at 6, 12, and 26 weeks, and then at half-year intervals up to 2 years. The primary study outcome, depression recovery, was measured with the Longitudinal Interval Follow-up Evaluation and defined as ≥8 weeks with no or minimal symptoms and little or no impairment.

**Results:** A total of 212 adolescents were randomized to treatment. Use of TAU options during the 104 weeks of follow-up was high and similar in the 2 groups, with more than half of patients receiving outpatient mental health services, 30–36% receiving school counseling, and 18–32% receiving antidepressants or other psychotropic medication. Fewer CBT patients received inpatient treatment during follow-up: 5% versus 11%.

The majority of patients in both groups recovered from depression. Young people who received CBT had significantly higher rates of recovery than those who did not. (See table.) The peak difference between the 2 groups was greatest at 15–20 weeks. The average number needed to treat (NNT)* was 6 for recovery immediately post-treatment and 10 during the second year of follow-up. Secondary outcome measures of depression symptoms also favored CBT, but other secondary measures, such as treatment satisfaction, substance use, and suicidal behavior, did not differ between treatments.

<table>
<thead>
<tr>
<th>Response and Recovery Rates</th>
<th>CBT plus TAU</th>
<th>TAU</th>
<th>Significance</th>
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<tbody>
<tr>
<td><strong>Diagnostic Response</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Week 52</td>
<td>91%</td>
<td>88%</td>
<td>p=0.03</td>
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<tr>
<td>Week 104</td>
<td>94%</td>
<td>92%</td>
<td>p=0.03</td>
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<tr>
<td><strong>Diagnostic Recovery</strong></td>
<td></td>
<td></td>
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<tr>
<td>Week 52</td>
<td>80%</td>
<td>69%</td>
<td>p=0.005</td>
</tr>
<tr>
<td>Week 104</td>
<td>89%</td>
<td>79%</td>
<td>p=0.003</td>
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</tbody>
</table>

*Response and Recovery Rates: CBT plus TAU and TAU.*
Discussion: Previous research shows a majority of adolescents with depression decline antidepressant medication or are non-adherent in primary-care settings. In the present study CBT was associated with modest effects and high NNTs, and many of the benefits over TAU were transient. Nevertheless, even temporary relief of symptoms for 1 year can have clinical and developmental benefits in this age group.


*See Reference Guide.*

**Tourette Syndrome in Children with ADHD**

There is a misperception that stimulants are contraindicated in patients with tic disorders because of their potential to cause or exacerbate tics. ADHD and Tourette syndrome (TS) are highly comorbid, with nearly 65% of young patients with TS also affected by ADHD. Although tics can present as an adverse effect of stimulants, given the high comorbidity of the disorders, emerging tics can be a symptom of TS, which typically manifests at a later age than ADHD. Stimulants remain an important option for treatment in these children as they can reduce tic severity and improve quality of life.

The authors describe 2 children, aged 8 and 10 years, with ADHD in whom tics developed after successful stimulant treatment. Both children eventually received a diagnosis of TS and received treatment with dexamethylenphedate plus either clonidine or risperidone. Both children experienced relief from ADHD and the majority of tic symptoms.

Few of the medications commonly used for tic disorders in children are FDA approved for that indication. The authors recommend starting with a nonstimulant, such as clonidine or guanfacine, particularly the newer long-acting guanfacine formulations approved for ADHD. These agents can relieve both ADHD and tic symptoms. Recent evidence indicates that stimulants can be used in children with TS without worsening tics and that a combination of methylphenidate–clonidine is effective. Second-generation antipsychotics are an additional option for treating tics, although close monitoring is needed for metabolic, endocrine, extrapyramidal, and other side effects. First-generation neuroleptics are highly effective for tic disorders but remain a second-line option.

Oluwabus I, Parke S, Ambrosini P: Tourette syndrome associated with attention deficit hyperactivity disorder: the impact of tics and psychopharmacological treatment options. *World Journal of Clinical Pediatrics* 2016;5 (February 8): 128–135. From Drexel University College of Medicine, Philadelphia, PA; and Yale School of Medicine, New Haven, CT. **Source of funding not stated. The authors declared no competing interests.**

**Common Drug Trade Names:** clonidine—Catapres; dexamethylenphidate—Focalin; guanfacine ER—Intuniv; methylphenidate—Ritalin; risperidone—Risperdal

**Stimulants in ADHD with DMDD**

Dose optimization of stimulants led to moderate-to-large improvements in problem behaviors in children with comorbid ADHD and disruptive mood dysregulation disorder.

**Background:** Children with ADHD and persistent irritability are increasingly being given mood stabilizers and atypical antipsychotics, despite concerns about these agents’ use in young patients. It is unclear whether the best treatment for these children is stimulants and behavioral therapy targeting the externalizing symptoms or mood stabilizers and antipsychotics targeting irritability and aggression.

**Methods:** Stimulant dose optimization was carried out as part of a larger study of a psychosocial treatment for comorbid ADHD and DMDD in 68 children, aged 7–12 years. Before psychosocial treatment, physicians assessed each child’s stimulant dosage and, if indicated, started and/or optimized the drug over a 6-week period. The subjects of the present report were 38
children who had stimulants started or adjusted and who continued to meet diagnostic criteria for DMDD. Efficacy of stimulant treatment was measured as change from baseline to week 6 in various measures of mood symptoms, disruptive behavior, ADHD symptoms, and function.

**Results:** A total of 11 children were switched from 1 class of stimulants to another, usually at a lower dose equivalent; 11 had a dosage change within the same class, and 16 were previously stimulant naive. Baseline mood ratings suggested mild-to-moderate manic-like and depressive symptoms. Stimulant optimization was associated with significant improvement in mood and depression (see table), but changes from baseline in the Young Mania Rating Scale were not statistically significant. Parent ratings for behavioral symptoms showed moderate baseline levels of ADHD and oppositional defiant disorder (ODD) symptoms as well as mild conduct disorder (CD) symptoms; all improved after dose optimization (see table), as did some but not all teacher symptom ratings. Clinician-rated and parent-rated functioning also showed improvement over the course of the study, mostly with moderate effect sizes. Larger improvements in parent-rated ADHD and ODD were observed in treatment-naive patients versus those already taking stimulants; however, effects were similar in the 2 groups for teacher ratings. Medication was well tolerated, with most adverse effects decreasing over the period of observation.

**Discussion:** The present study results suggest that stimulants may be a reasonable first-line option for patients with comorbid ADHD and DMDD. It should be noted that escalating to the maximum tolerable dose of a stimulant was less effective than switching to a lower dose of a different agent. However, residual impairment indicates that additional treatment is needed to optimize functioning.

| Mean mood, behavioral, and ADHD symptom scores before and after stimulant optimization |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Measure                          | Baseline | Endpoint | Significance | Effect Size |
| Mood Severity Index              | 24.2     | 21      | p<0.001      | 0.55          |
| Children’s Depression Rating Scale—Revised | 34.3     | 30.9    | p<0.001      | 0.61          |
| Disruptive Behavior Disorders Rating Scale for ADHD | 35.2     | 26.3    | p<0.001      | 0.95          |
| Disruptive Behavior Disorders Rating Scale for ODD | 14.5     | 11.9    | p<0.001      | 0.50          |
| Disruptive Behavior Disorders Rating Scale for CD | 5.3      | 3.3     | p<0.001      | 0.65          |
| Children’s Global Assessment Scale | 54.6     | 56.8    | p=0.03       | —             |

**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:** 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.