Optimizing Stimulants Improved Aggression

Individualized stimulant optimization improved aggression in nearly half of a group of children with ADHD, precluding the need for adjunctive treatment.

**Background:** Treatment guidelines for ADHD with aggression recommend starting with a stimulant plus behavioral therapy and adding an antipsychotic if aggression persists. However, the use of antipsychotics for disruptive behaviors appears to be increasing.

**Methods:** The 65 study subjects were children, aged 6–13 years (mean age, 9 years), with ADHD and comorbid oppositional defiant disorder or conduct disorder who had significant aggressive behavior and a history of insufficient stimulant response. All participated in family-based behavioral therapy and underwent a stimulant monotherapy optimization protocol beginning with 18 mg/day triphasic methylphenidate (*Concerta*). Stimulant therapy was titrated weekly based on behavioral assessments and tolerability. Children who could not tolerate the methylphenidate formula could be switched to a biphasic-release preparation (*Metadate*), and those who had little or no improvement were switched to mixed amphetamine salts (*Adderall XR*). Parents completed the Retrospective-Modified Overt Aggression Scale (RMOAS) at each study visit. Children who achieved a RMOAS score of ≤ 16 for at least 3 weeks with optimized treatment were considered responders, while those whose score remained above 16 were considered to have refractory aggression and adjunctive medication was considered.

**Results:** After a mean treatment duration of 63 days, stimulant monotherapy reduced aggression sufficiently to prevent adjunctive medication use in 32 of the 65 children (49%). Most of these children (84%) achieved response with triphasic-release methylphenidate. In contrast, 51% of children with refractory aggression required a switch to the biphasic preparation or to mixed amphetamines. Average dosages were lower among responders (e.g., 52 vs 64 mg/day *Concerta*), and they received significantly fewer behavioral therapy sessions than children with stimulant-refractory aggression (3 vs 7; p<0.01).

Baseline levels of aggression and ADHD symptom scores were associated with treatment response; children with higher scores were more likely to have refractory aggression. Aggression was not sufficiently improved in any of the 4 patients with a comorbid depressive...
disorder. Girls, who comprised <25% of the sample, were significantly more likely to respond to optimized stimulant monotherapy (odds ratio,* 8.9; p=0.02). Regardless of aggression improvement, children in both groups showed significant reductions in ADHD symptoms.

**Discussion:** Individualized stimulant optimization can reduce the need for adjunctive antipsychotic medication in children with ADHD and aggression. Boys, particularly those with higher baseline symptom severity, may be more likely to require adjunctive treatment.

Blader J, Pliszka S, Jensen P, Scholler N, et al: Stimulant-responsive and stimulant-refractory aggressive behavior among children with ADHD. *Pediatrics* 2010; doi 10.1542/peds.2010-0086. From Stony Brook University School of Medicine, N.Y.; and other institutions. Funded by the NIH; and other sources including Abbott Laboratories. All study authors disclosed commercial relationships with pharmaceutical-industry sources.

*See Reference Guide.

**Early Predictors of Atomoxetine Response**

A previously reported analysis of pooled data found that evidence of improvement in the first 4 weeks, indicated by a reduction in ADHD Rating Scale (ADHD-RS) score, predicted atomoxetine (*Strattera*) response in children with ADHD.¹ Now, another analysis extends those findings to suggest that improvement in single ADHD-RS items, as early as week 1, may predict outcomes.²

**Methods:** Data from 5 randomized controlled atomoxetine trials, comprising more than 500 treated patients, was used to develop models for predicting atomoxetine response. Patient ages ranged from 6 to 18 years, and acute treatment durations averaged 6–9 weeks. Dosages and titration schedules varied. Each of the 18 ADHD-RS items was evaluated along with other potential predictors (e.g., age, gender, ADHD subtype).

**Results:** Early improvement in parent-rated ADHD-RS item 15 (“easily distracted”) predicted atomoxetine response at 6 weeks. Nearly 80% of children (85% of a test group, and 74% and 73% of 2 validation groups) with a ≥1 point improvement on the item at week 1 responded to atomoxetine treatment. Item 1 (“fails to give close attention or makes careless mistakes”) and item 10 (“on the go”) also predicted treatment response. About 75% of patients with a ≥1 point change on either of these items at week 2 or 3 went on to achieve treatment response by week 6. Age, gender, and ADHD subtype were not predictive of response.

**Discussion:** Time constraints may prohibit administration of the entire ADHD-RS at each clinical visit. These results suggest that scoring only 3 of the 18 items within the first 3 weeks of treatment could help predict whether patients will respond to atomoxetine.


**Cognitive Deficits and Self-Perception in ADHD**

Cognitive deficits partially explain why some children with ADHD overestimate their competence in academic, behavioral, or social performance. A lack of awareness of poor competence may limit the ability of some children with ADHD to respond to feedback and improve over time. Measures to improve these children’s self-awareness may be helpful.

**Methods:** Study participants were 184 children, aged 7–11 years, with ADHD and 88 controls without ADHD. Children with predominantly inattentive-type ADHD were not studied because positively-biased self-perception is not associated with this subtype. While unmedicated, participants and their teachers completed the Self-Perception Profile for Children,
which rates perceptions of competence in different domains. Those with ADHD were grouped according to whether or not their self-rating exceeded that of their teacher by more than about 1 standard deviation. The children without ADHD were classified as controls since very few exhibited positive self-rating bias. Cognitive function was assessed using the Woodcock-Johnson Tests of Cognitive Abilities, and depression using the Children’s Depression Inventory.

**Results:** Children's self-evaluations of academic, social, and behavioral conduct were assessed separately. In general, children with ADHD and high positive bias had more cognitive impairment than either controls or children with ADHD lacking high bias. Controls had greater abilities in most areas of cognitive function than children with ADHD, regardless of their level of bias.

In an evaluation of academic performance, ADHD without bias was associated with greater ability in executive processes compared to ADHD with high bias. High bias in social performance was associated with a broader pattern of cognitive deficits that also included working memory, broad attention, and cognitive fluency. In a further analysis, cognitive deficits were shown to be partial mediators of the effect of ADHD on self-assessment bias in all 3 areas of function. Depression was predictive of less positive self-assessment bias.

**Discussion:** Previous studies have shown cognitive deficits are associated with poor insight of competency in other clinical populations. The present analysis suggests that these deficits partly explain the variation in self-assessment bias among children with ADHD.

McQuade J, Tomb M, Hoza B, Waschbusch D, et al: Cognitive deficits and positively biased self-perceptions in children with ADHD. *Journal of Abnormal Child Psychology* 2010; doi 10.1007/s10802-010-9453-7. From the University of Vermont, Burlington; and other institutions. Funded by the NIMH. This early release report did not include disclosure of competing interests.

### Suppressing Tics

Drugs representing many classes are available for treatment of moderate-to-severe tics, but none are highly effective, according to a literature review. Patients with moderate-to-severe tics that cause pain or social or functional impairment may benefit from medical tic suppression, despite its shortcomings. None of the agents currently used for tic suppression were designed or marketed specifically for this indication.

Haloperidol, pimozide, and risperidone are the only antipsychotic medications with Class A evidence (i.e., ≥2 placebo-controlled trials with positive results) for tic suppression, and haloperidol and pimozide have FDA approval for this indication. These 3 agents have similar overall efficacy, reducing tic scores by 35%–65% in controlled trials. Other high-potency neuroleptics have similar reported effects but are not as well studied. Fluphenazine is preferred by some because its drug interaction and cardiac profiles are more benign. Aripiprazole, ziprasidone, and olanzapine have limited evidence of tic reductions, while quetiapine and clozapine have little or no evidence supporting their use. Overall, the use of these antipsychotics is limited by concern about side effects such as drug-induced movement disorders for the older agents and metabolic effects for the atypicals.

No non-neuroleptic agents were judged to have class A evidence for efficacy in tic suppression, but clonidine, guanfacine, pergolide (now off the U.S. market) and botulinum toxin have class B evidence. Clonidine was investigated in a large study of children with tic disorders and ADHD, which showed only modest efficacy consisting of a 25% tic reduction at 16 weeks. A review suggested guanfacine reduces tic scores by 30% relative to placebo. Atomoxetine reportedly reduced tics by about 25% in a group of children with ADHD. In small trials, levetiracetam and topiramate significantly reduced tic scores. Dopamine agonists have modest effects, and the acetylcholinesterase inhibitor donepezil reduced tics by 30–40% in patients who completed a small trial.
Case reports and open-label studies suggest botulinum toxin injection into the muscles where tics occur can be highly effective, but the invasiveness of administration, high costs, and risk of side effects limit its use to severely affected patients who do not respond to other treatments. Deep brain stimulation has been shown to be effective in case reports and small case series in adults, but it is not recommended for young patients. The procedure is invasive, and surgical complications can occur. Transcranial magnetic stimulation (TMS) is noninvasive, but studies to document safety and efficacy are needed.

A good deal of research has investigated treatment of tics. No currently prescribed medication is highly effective at controlling moderate-to-severe tics, but many may help to some degree.

Wu S, Harris E, Gilbert D: Tic suppression: the medical model. *Journal of Child and Adolescent Psychopharmacology* 2010; 20 (August):263–276. From Cincinnati Children's Hospital Medical Center, Ohio. **One study author disclosed an agreement with Otsuka Pharmaceuticals to fund research of aripiprazole in tic disorders.**

*Drug Trade Names:* aripiprazole—*Abilify*; atomoxetine—*Strattera*; botulinum toxin—*Botox*; clonidine—*Catapres*; clozapine—*Clozaril*; donepezil—*Aricept*; fluphenazine—*Prolixin, and others*; guanfacine—*Tenex*; haloperidol—*Haldol*; levetiracetam—*Keppra*; olanzapine—*Zyprexa*; pergolide (no longer available in the U.S.)—*Permax*; pimozide—*Orap*; quetiapine—*Seroquel*; risperidone—*Risperdal*; topiramate—*Topamax*; ziprasidone—*Geodon*.

### D-Cycloserine Enhanced CBT Response

Adding D-cycloserine (*Seromycin*) to cognitive-behavioral therapy produced medium-to-large positive effects on several measures of obsessive-compulsive disorder (OCD).

**Background:** The NMDA receptor plays an important role in fear extinction, and the partial NMDA agonist D-cycloserine has been shown to enhance extinction of learned fear. Pretreatment with D-cycloserine in adults undergoing CBT has produced rapid reductions in obsession-related fear.

**Methods:** Thirty patients, aged 8–17 years, with a primary diagnosis of OCD were enrolled in the randomized study. All participants received 10 CBT sessions beginning with psychoeducation and cognitive training, and progressing to exposure and response prevention (ERP). In addition, they were randomized to D-cycloserine and placebo groups. One hour before each session that included ERP (numbers 4–10), parents gave their child D-cycloserine or placebo. Children weighing <100 lbs received 25 mg D-cycloserine, and heavier children received 50 mg.

**Results:** Children in both groups improved, but response was stronger in patients pre-treated with D-cycloserine. Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS) scores, the primary efficacy measure, decreased by 72% with D-cycloserine augmentation, compared with 58% in the placebo group. Clinical Global Impression–Severity* ratings improved from moderate-to-markedly ill at baseline to borderline ill with D-cycloserine and to mildly ill with placebo. The effect sizes* for active augmentation were 0.31–0.47 for primary outcomes. Between-group differences on these measures did not reach statistical significance, but because the sample size was small the study may have been underpowered to detect such differences. No adverse effects of D-cycloserine were reported.

**Discussion:** Consistent with adult reports, adding D-cycloserine to CBT enhanced response in this small group of young patients. The results of this preliminary study suggest D-cycloserine augmentation may be a safe and effective alternative to SSRI augmentation for pediatric OCD.

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

Storch E, Murphy T, Goodman W, Geffken G, et al: A preliminary study of D-cycloserine augmentation of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. *Biological Psychiatry* 2010; doi 10.1016/j.biopsych.2010.07.015. From the University of South Florida, St. Petersburg; and other institutions. **Funded by the NIMH; and the National Alliance for Research on Schizophrenia and Affective Disorders (NARSAD). Several study authors disclosed commercial relationships with pharmaceutical-industry sources.**

*See Reference Guide.*
**Trends in Pharmacotherapy for Behavior Disorders**

Several studies have suggested large increases in the prescription of psychotropic medications for children in recent years. A record review from a specialty behavior disorders clinic suggests the increase, if it exists, is not driven by increased prescribing for disruptive behaviors.

**Methods:** Records were reviewed from a behavioral pediatrics clinic in rural Iowa to identify otherwise normally developing children (n=709), aged ≤10 years, referred for conduct and/or oppositional behavior (designated as disruptive behavior disorders or behavior management issues, problems, or concerns). Trends in medication use were tracked from 2001 to 2007.

**Results:** The number of children referred to the center increased by 39% over the study period. While the number of children prescribed psychotropics increased over time, the overall percentage of patients receiving medication did not differ between 2001 and 2007. There were no consistent increases in the percentage of patients receiving stimulants, antipsychotics, antidepressants, or adrenergic agents. (See table.)

### Children Using Psychotropic Medications

<table>
<thead>
<tr>
<th>Year</th>
<th>Stimulants</th>
<th>Antidepressants</th>
<th>Antipsychotics</th>
<th>Adrenergics</th>
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<td>4%</td>
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<td>16%</td>
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<td>5%</td>
<td>0%</td>
<td>1%</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Discussion:** The authors note that the study sample was small and patients were largely from rural areas. Geographic differences could account at least in part for the differences between the current results and those of previous studies.

Seyfer D, Van Dyke D, Wacker D, McConkey S, et al: Observations in psychotropic medication usage in patients with behavior disorders presenting to a specialty clinic. *Clinical Pediatrics* 2010; doi 10.1177/0009922810379500. From the University of Iowa Hospitals and Clinics, Iowa City. **Funded by the NIH. The authors report no competing interests.**

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**Pineal Tumor and Prodromal Psychosis**

A 17-year-old male was referred to the UCLA Center for Assessment and Prevention of Prodromal States because of subthreshold psychotic symptoms. The patient’s early development was unremarkable, but at age 13 he began to exhibit cognitive and behavioral declines in addition to unusual behaviors including idiosyncratic hand gestures, excessive consumption of salty foods, and checking compulsions. Treatment with fluvoxamine (*Luvox*) did not improve his symptoms. The patient received psychotherapy in the ensuing years. However, verbal expression continued to decline and unusual thought content and other positive symptoms of psychosis developed. MRI, although incomplete and without contrast, was unremarkable and he was presumed to be in a prodromal state.

During the course of his psychiatric treatment, he continued to exhibit stereotyped gestures and began engaging in self-injurious behavior. Polydipsia also developed. He eventually lost oriene-
tation to time and date and began to wander away from home. He also displayed symptoms not characteristic of prodromal schizophrenia including dragging of his left foot. Psychotherapy and multiple antipsychotic regimens were ineffective. He progressed to overt psychosis, and long-term placement was considered.

As part of the entry examination, the patient underwent another MRI (with and without contrast). A pineal tumor was identified as well as evidence of a small left-sided basal ganglia stroke. Following oncological treatment, the psychotic symptoms resolved and the patient’s cognitive skills and behavior improved to near premorbid levels. Polydipsia resolved, but he continued to experience mild depression, some unusual thought content, and motor function impairment. Two years after his initial presentation for prodromal evaluation, he returned to school and had no psychotic symptoms.

There have been few reports of psychosis associated with subcortical tumors in young patients, and pineal gland tumors are rare. However this case highlights the potential for pineal gland and subcortical abnormalities to induce psychotic-like behaviors.

Mittal V, Karlsgodt K, Zinberg J, Cannon T, et al: Identification and treatment of a pineal region tumor in an adolescent with prodromal psychotic symptoms. American Journal of Psychiatry 2010;167 (September):1033–1037. From the University of California, Los Angeles. The study authors received grant support from the NIH; NARSAD; and other sources, but report no competing interests.

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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.

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.

Odds Ratio: A comparison of the probability of an event in two groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

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.

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