Comorbid ADHD appears to be common in patients with juvenile bipolar disorder, and its presence may adversely affect clinical course. In these patients, aripiprazole (Abilify) monotherapy was recently found to have a large positive effect on mania and it did not affect symptoms of ADHD.

Methods: Patients aged 8–17 who were experiencing an acute manic or mixed episode of bipolar disorder and who had comorbid ADHD were eligible for the controlled pilot study. Patients who had not received any medication in the previous 4 weeks (n=43) were randomized to 6 weeks of aripiprazole or placebo. The aripiprazole starting dose was either 2 mg/day or 5 mg/day depending on weight (with the cutoff between doses at 110 lbs). Aripiprazole was increased weekly to a maximum of 20 mg/day. The Young Mania Rating Scale (YMRS) was the primary outcome measure and was administered weekly. ADHD symptoms were assessed using the Swanson, Nolan, and Pelham Scale-Version IV (SNAP-IV).

Results: At 6 weeks, the reductions in YMRS score were significantly greater in the aripiprazole group. Baseline scores of 36 in the aripiprazole group and 41 in the placebo group were reduced to 9 and 21, respectively (p=0.02; effect size,* 0.8). Neither the aripiprazole nor the placebo group showed a significant change in SNAP-IV total score. Both parent ratings of mania and clinician-rated Clinical Global Impression-Severity scores (both secondary outcomes) were significantly improved with aripiprazole. Depressive symptoms were not affected by treatment.

Two patients withdrew from the study: 1 in the placebo group refused to continue after week 4 and 1 treated with aripiprazole who experienced severe extrapyramidal symptoms. Adverse effects that occurred in >50% of the aripiprazole-treated patients were somnolence; tiredness; appetite changes; headache; nausea; sialorrhea; anxiety; cough; and sweating. No adverse effect was significantly more common with aripiprazole than placebo. Weight gain was similar in the aripiprazole and placebo groups (2.6 vs 1.6 lbs), but the treatment duration was short.

Discussion: Because this is the first randomized controlled trial of aripiprazole in young patients with comorbid bipolar disorder and ADHD, the results need to replicated. It should be noted
that aripiprazole is approved for use in patients aged 10 years and older. This study included patients as young as 8 years. Although the number of patients aged <10 was not specified, a secondary analysis of those aged ≥10 years was conducted and the results were unchanged.

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


*Reference Guide Item.*

### Long-Acting Methylphenidate in Preschoolers

A pilot study found long-acting beaded methylphenidate (*Ritalin LA*) to be safe and effective in a small group of preschool children with ADHD.

**Background:** Pharmacological treatment of ADHD in preschool children has received little study. The large NIMH-funded PATS established methylphenidate as effective in this population, but a long-acting formula was not evaluated and is not approved for use in children under age 6 years. The ability to sprinkle *Ritalin LA* on food without compromising its efficacy and the once daily dosing are clear advantages. However, because there are fewer dosing options, tolerability could be problematic.

**Methods:** Children aged 4–5 years with ADHD who were referred to the N.Y. State Psychiatric Institute (n=11; 9 males) were included in the study. No child had previously received pharmacological treatment for ADHD and all had Clinical Global Impression (CGI) Severity ratings of "markedly ill." Patients received 10 mg/day long-acting methylphenidate, and the dose could be increased to 20 or 30 mg/day as needed. Parents underwent individual parent-training sessions. The children were evaluated over the 4 weeks of treatment with multiple standardized clinician- and parent-completed measures.

**Results:** After 4 weeks, the severity of ADHD was significantly improved: CGI-Severity ratings improved from "markedly ill" to "mildly ill" and 6 of the children (55%) were rated as "much improved" on the CGI-Improvement scale. Four patients were unchanged and 1 was "minimally improved." Parent-rated Swanson, Nolan, and Pelham Questionnaire (SNAP-IV) ADHD composite scores were also significantly reduced from 2.3 to 1.1 (p<0.01). Clinician-rated global functioning was also significantly improved with treatment.

The most common adverse effect, decreased appetite, affected 7 patients and continued to study end in 5. Sleep difficulty, emotional lability, and GI pain were also common. Three patients did not complete the study because of intolerable adverse effects: stomach ache and emesis; increased irritability; and sedation. There were no significant changes in blood pressure, pulse, or weight. The authors note that the availability of 10-mg capsules as the smallest dose form can cause titration difficulties. After completion of the study, several patients continued treatment and when tolerability was an issue during further titration, parents were instructed to open a capsule and administer half of its contents (5 mg). This strategy led to positive outcomes.

**Injectable Risperidone in Bipolar Disorder**

Medication nonadherence is a common cause of treatment failure in bipolar disorder. The FDA recently approved the long-acting injectable formulation of risperidone (*Risperdal Consta*) for maintenance treatment of bipolar I disorder in adults.\(^1\) Although not approved for pediatric use, a case series shows injectable risperidone was both safe and effective in 3 young patients with bipolar disorder.\(^2\)

The first patient, an 11-year-old male, had a history of school phobia and major depressive disorder (MDD). Treatment with sertraline produced a switch to mania, and the symptoms persisted after sertraline was stopped. Oral risperidone monotherapy produced significant improvement, but the patient was intermittently compliant with treatment. His Clinical Global Impression Severity (CGI-S) score\(^*\) was 6 and his Children’s Global Assessment Scale (CGAS) score\(^*\) was 31, indicating severe impairment. Long-acting risperidone injections administered at 25 mg every other week produced significant improvement that was evident after the third injection. After the fifth injection, the patient’s aggressive behavior and manic symptoms were controlled, his CGI-S score was 3, and his CGAS score was 61. He was successfully switched to 3 mg/day risperidone monotherapy and continued doing well.

The second patient, a 14-year-old male with ADHD, had been treated with sertraline for a depressive episode at age 6. Both sertraline and a later trial of fluoxetine produced agitation, euphoria, a hyperenergized state, and a decreased need for sleep. Symptoms persisted after SSRI discontinuation and he began to exhibit a hypererotic attitude and aggressiveness. Between the ages of 7 and 13 years he underwent multiple medication trials that failed to control his symptoms. Oral risperidone monotherapy initially controlled the mania but his compliance was intermittent and hypothyroid and metabolic syndrome-like symptoms developed. When he was started on 25 mg long-acting injectable risperidone every other week his CGI-S score was 7 and his CGAS score was 25. After 5 injections, his externalizing behavior was controlled, and after 10 injections his CGI-S score was 3 and his CGAS score was 71. At the time of the report he had continued treatment uneventfully for 9 months without recurrence of metabolic effects.

The third patient, also a 14-year-old male, had received a diagnosis of MDD at age 11 years. Fluoxetine treatment produced a transient mixed state and then a full manic episode with euphoria, hyperenergy, talkativeness, and reduced need for sleep. Improvement was noted with the combination of oral risperidone and carbamazepine, but he complied with the regimen irregularly. At age 14 he was started on 25 mg long-acting injectable risperidone every other week. His CGI-S score decreased from 6 to 3, and his CGAS score improved from 31 to 71. He has remained stable over 6 months of continued treatment.

All 3 patients tolerated the risperidone injections. Weight gain, extrapyramidal symptoms, and metabolic effects did not appear to be a concern. There were no significant cognitive complaints or adverse hormonal effects.

\(^1\)FDA grants approval for use of risperdal consta as both a monotherapy and adjunctive therapy in the maintenance treatment of bipolar I disorder [press release]. Titusville, N.J.; Janssen Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.; May 18, 2009.

\(^2\)Fu-I L, Boarati M, Stravogiannis A, Wang Y-P: Use of risperidone long-acting injection to support treatment adherence and mood stabilization in pediatric bipolar patients: a case series. *Journal of Clinical Psychiatry* 2009;70 (April):604–606. From the University of Sao Paulo, Brazil. Two study authors disclosed financial relationships with pharmaceutical-industry sources; the remaining 2 authors disclosed no potential conflicts of interest.

*Drug Trade Names:* carbamazepine—*Epitol, Tegretol*; fluoxetine—*Prozac*; risperidone, oral—*Risperdal*; risperidone, long-acting injection—*Risperdal Consta*; sertraline—*Zoloft*

*Reference Guide Item.*
**Predicting Atomoxetine Response**

A retrospective analysis of pooled data from 6 manufacturer-sponsored trials found that some improvement in the first 4 weeks of atomoxetine (*Strattera*) treatment was associated with response.¹ No other demographic or illness variables predicted response.

**Methods:** The Integrated Data Exploratory Analysis (IDEA) study evaluated response in patients who received double-blind atomoxetine (n=618) in a randomized controlled trial. All 6 studies used the ADHD Rating Scale (ADHD-RS) as the primary efficacy measure. Patients were stratified by category of response where a ≥40% decrease in ADHD-RS score indicated good clinical response, a 25–39% reduction indicated minimal response, and a <25% decrease indicated nonresponse. Patient age, gender, ADHD subtype, previous stimulant exposure, CYP metabolism status, comorbidity, and baseline ADHD-RS scores were evaluated as potential predictors of response.

**Results:** Of the 618 patients who received atomoxetine, 60% experienced at least minimal response, and 47% of the total sample was judged to have good clinical improvement at the end of acute treatment (6–9 weeks). No baseline patient, demographic, or illness characteristics were found to predict later response. The only identified association was between early improvement (≥25% decrease in ADHD-RS score by week 4) and response. Having at least minimal response was strongly predictive of having good clinical improvement at study end. The positive predictive value* was 75% and the negative predictive value* was 79%.

**Discussion:** A recent study of nonpsychotic depression also found antidepressant-associated improvement at 4 weeks was the best predictor of later remission.² Taken together, these results suggest the decisions regarding treatment changes in ADHD and in depression could be made earlier than current recommendations suggest.


*Reference Guide Item.

**CBCL Profile Predicts Bipolar Disorder**

The Child Behavior Checklist–Pediatric Bipolar Disorder (CBCL-PBD) profile, with high scores in attention problems, aggressive behavior, and anxious-depressed characteristics, predicted the onset of bipolar disorder and other impairments in a group of children with ADHD.

**Background:** The DSM-IV criteria for diagnosing bipolar disorder in adults are clear, but controversy remains about how to apply them to pediatric patients. The ability to predict in which patients bipolar disorder is likely to develop could improve recognition and early treatment strategies.

**Methods:** Patients (aged 6–18 years) with ADHD were identified from 2 longitudinal case-control family studies in ADHD. As part of the baseline evaluation, 204 mothers administered the CBCL to their child. The CBCL-PBD score was considered positive if the sum of the 3 subscales was ≥210 (a cutoff previously shown to maximize the discriminatory performance of the test). Patients received periodic psychiatric assessments using standardized age-appropriate instruments to a maximum age of 25 years (mean follow-up, 7 years).

**Results:** Scores indicated a positive CBCL-PBD profile in 28 of the children (14%). Those with positive scores were generally of lower socioeconomic status than those with lower scores, and
had increased baseline rates of major depressive disorder, oppositional-defiant disorder, and conduct disorder. Gender did not appear to affect scores.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CBCL-PBD profile</th>
<th>Hazard ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive (n=28)</td>
<td>Negative (n=176)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>36%</td>
<td>22%</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>56%</td>
<td>29%</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>60%</td>
<td>27%</td>
</tr>
<tr>
<td>Psychiatric hospitalization</td>
<td>73%</td>
<td>13%</td>
</tr>
</tbody>
</table>

By age 25, the incidence of bipolar disorder was increased in patients with positive CBCL-PBD scores, as were rates of other outcomes often associated with bipolar disorder including subsequent hospitalization for mood disorders (see table). Positive scores also predicted greater impairment in psychosocial functioning. Patients with positive scores did not have significantly higher rates of multiple anxiety disorders, oppositional defiant disorder, substance use disorder, or smoking.

**Discussion:** The CBCL-PBD score was previously shown to predict current pediatric bipolar disorder, though not consistently in all studies. In the present study, bipolar disorder did not develop in the majority of patients with a positive score, and the test should not be used to diagnose bipolar disorder. However, a positive score can alert clinicians that a patient is at high risk for bipolar disorder and other impairments.


*Reference Guide Item.*

**ADHD Pharmacotherapy Affects Academic Achievement**

Medicating elementary school children with ADHD appears to improve their level of academic achievement over time.

**Background:** Treating ADHD has been shown to improve some measures of academic function, but methodological issues such as small sample sizes, short treatment durations, and broad outcome measures limit the clinical usefulness of study results. Few medication trials that measured academic achievement over time have been conducted.

**Methods:** The Early Childhood Longitudinal Study tracks the academic performance of a nationally representative sample of U.S. children. Data on children with ADHD entering kindergarten in 1998 (n=1195) was used for the present analysis. The children were administered grade-appropriate standardized math and reading tests that were created for the study on 5 occasions between kindergarten and grade 5. Parents were asked after the last testing session if their child was currently taking an ADHD medication, and if so, how long they had been medicated. Effects of gender and participation in an individualized education program (IEP) were examined as potential moderators.
Results: Complete data, including ≥2 test scores and medication information, was available for 594 children. Math scores were 3 points higher in the children who received medication than in those who did not (p<0.05), regardless of duration of treatment. Reading scores were 5 points higher (p<0.01) in children after they received medication for at least 1 year. However, both math and reading scores were still lower in medicated children than in children without ADHD. Gender did not appear to affect educational achievement, but children with an IEP over ≥3 periods had lower math and reading scores.

Study Limitations: Information on ADHD diagnosis and medication status was collected by parent report, and dosages were not considered. In addition, continuity of medication treatment was assumed and adherence gaps were not investigated, and it was assumed that a child not medicated at the final testing session had not received pharmacotherapy at any point.

Discussion: Early academic achievement is critical to later school success, and ADHD is associated with deficits in academic achievement. Medicating children with ADHD appears to improve both math and reading achievement, but not to a sufficient degree that their average test scores match those of their non-ADHD peers.


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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.

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 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.

Hazard ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that one group has half the risk of the other group.

Positive and Negative Predictive Values: The positive predictive value is the proportion of patients with positive test results who are correctly diagnosed. The negative predictive value is the proportion of patients with negative test results who are correctly diagnosed.

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.