Evidence-Based Treatment of Aggression in ADHD

According to the evidence-based review, aggression in ADHD is best treated by reducing the overall severity of ADHD. Target symptom-based treatment is not well supported, but should be considered if the effects of stimulants and psychosocial treatment are inadequate.

As part of a quality improvement project, a literature review identified 16 available practice guidelines, meta-analyses, and systematic reviews of the treatment of aggression in patients aged ≤18 years with ADHD. After careful examination of the data including measures of evidence quality, 3 recommendations were developed.

- ADHD medications should be the first-line treatment for aggression.
- Patients should receive psychotherapy in addition to medication.
- When aggression persists despite adequate ADHD medication and psychosocial treatment, risperidone or other symptom-targeted medication may be added.

Stimulants, the best-studied class of medications, are associated with moderate to large effect sizes in reducing aggression. One meta-analysis of 28 controlled stimulant trials in 683 patients concluded that the agents significantly improved ratings of overt and covert aggression. The mean quality rating of these studies was 5.7 (maximum score, 7). Two other large meta-analyses support the use of stimulants to reduce aggression, with comparable effect sizes. Effect sizes for alpha-2 agonists and antidepressants in aggression are small to moderate. Atomoxetine showed only a small effect on aggression in a meta-analysis, but this result may be limited to a dose-response relationship.

If stimulants are used, the evidence indicates patients should receive an adequate trial before moving on to another approach to control aggression. Stimulants should be started at the minimal recommended dose for 2 to 4 weeks and then titrated with sufficient time between increments to observe the effects on aggression.

Psychotherapy is supported by a "moderate" grade of evidence. Behavior therapy is effective in controlling aggression in youth, but studies specific to ADHD are lacking and effects in combination with ADHD medication are unknown.

Continued
Risperidone can be added if ADHD symptoms are controlled with medications and psychotherapy but significant aggression remains. However, evidence for this recommendation is of low-to-moderate quality. Other atypical antipsychotics, though not well studied, may also be effective. If symptoms persist with atypical antipsychotic augmentation, a trial of lithium, divalproex, or clonidine can be considered.

List B, Barzman D: Evidence-based recommendations for the treatment of aggression in pediatric patients with attention deficit hyperactivity disorder. *Psychiatric Quarterly* 2010; doi 10.1007/s11126-010-9145-z. From Cincinnati Children’s Hospital Medical Center; and the University of Cincinnati, Ohio. *Author disclosure not provided in the early release of this report.*

*Drug Trade Names*: atomoxetine—*Strattera*; clonidine—*Catapres*; divalproex—*Depakene, Depakote*; risperidone—*Risperdal*

### CYP and Atomoxetine Metabolism

Impaired cytochrome P450 metabolism of atomoxetine (*Strattera*) can delay response, which can lead to dosage increase and subsequent adverse effects.

**Background:** Atomoxetine is metabolized mainly via the cytochrome P4502D6 (CYP2D6) pathway and CYP2C19 is a minor pathway. Polymorphisms in these pathways can affect atomoxetine response. CYP activity falls into 4 main categories: ultrarapid metabolizers exhibit extremely high CYP2D6 activity; extensive metabolizers display normal activity; intermediate metabolizers possess lower enzyme activity; and poor metabolizers exert no activity. About 20–30% of Caucasian patients fall outside the "normal activity" range.

**Methods:** Records for 100 outpatients with ADHD treated by a single neurologist were reviewed for potential evidence of CYP polymorphisms. Ten children, aged 8–15 years, were identified who had either late-onset therapeutic effects (i.e., >9 weeks) or adverse effects such as GI complaints, sleep disorders, malaise, or mood instability. These 10 children underwent CYP450 genotyping.

**Results:** Genotyping found compromised CYP2D6 function in 6 of the 10 patients. No patient was found to be an ultrarapid or poor metabolizer. Of the patients with compromised CYP2D6 metabolism, 4 discontinued atomoxetine because of adverse effects and were not willing to undergo a lowered dose rechallenge. The other 2 intermediate CYP2D6 metabolizers had improved response after the atomoxetine dose was reduced. CYP2C19 function was found to be compromised in 4 patients, all of whom were classified as intermediate metabolizers. Of these patients, 1 had discontinued treatment because of adverse effects and 3 responded well to a reduced dose.

**Discussion:** In order to prevent dropouts and to optimize dosing, the study authors recommend pretreatment genotyping before prescribing atomoxetine. They do, however, acknowledge the cost factors involved in genotyping and thus the need for a cost/benefit analysis.


### Western Diet and ADHD

In a population-based cohort of adolescents, analysis of food frequency questionnaires shows western dietary patterns are associated with increased risk of ADHD.

**Methods:** The Western Australian Pregnancy Cohort included >2800 children followed longitudinally from birth. At the 14-year follow-up, sociodemographic and lifestyle information...
was collected and 1172 adolescents and their primary caregiver completed food frequency questionnaires. With the food frequency measure, more than 200 specific foods were grouped into 38 categories, and 2 major eating patterns were identified: healthy and western. The healthy eating pattern included higher fatty acid, fiber, and folate intakes, while the western pattern was characterized by higher intake of fats, refined sugar, and sodium. Presence of ADHD was recorded based on caregiver report of the adolescent having ever received the diagnosis.

**Results:** Adolescents with primarily western diets were significantly more likely to have ADHD (odds ratio* [OR], 2.1; p<0.05). Specific foods in the western diet that contributed to the increased risk included soft drinks (OR, 2.4), red meats (OR, 2.3), high-fat dairy products (OR, 2.0), chips (OR, 2.0), "take-out" foods (OR, 1.9), and processed meats (OR, 1.9). Western dietary patterns were associated with both the inattentive and combined subtypes of ADHD, but after adjustment for confounding factors the association with inattentive ADHD was no longer significant.

**Discussion:** Because of the cross-sectional nature of the data, a causal relationship between the western diet and ADHD cannot be confirmed. The association may be bidirectional, in that adolescents with ADHD experiencing emotional distress may consume more fat-rich snacks in an effort to self-soothe. It is also possible that poor family functioning, which often accompanies ADHD, may drive food choices.

Howard A, Robinson M, Smith G, Ambrosini G, et al: ADHD is associated with a "western" dietary pattern in adolescents. *Journal of Attention Disorders* 2010; doi 10.1177/1087054710365990. From the University of Western Australia, West Perth; and Curtin University of Technology, Perth, Australia. Funded by the Raine Medical Research Foundation at the University of Western Australia; and other sources. The authors declare they have no conflicts of interest relevant to the study.

*See Reference Guide.

**Fetal Antidepressant Exposure and ADHD**

Serotonin reuptake inhibitor use early in pregnancy can increase the risk of cardiac anomalies and use later in pregnancy can increase the risks of preterm delivery, low birth weight, respiratory distress syndrome, and neonatal behavioral withdrawal syndrome. SSRI use in pregnancy has also been associated with deficits in motor development, but does not appear to affect cognition, language, temperament, or externalizing behaviors. Less is known about the effects of in utero antidepressant exposure on long-term neuropsychological development of the offspring. The present study used linked claims-based data from >38,000 U.S. families to evaluate the effects of parental mental illness and in utero antidepressant exposure on development of ADHD by age 5 years.

A total of 431 children had evidence (e.g., clinical diagnosis or treatment) of ADHD in their medical record before the age of 5. ADHD was not more likely to develop in children who were born preterm or with low birth weight, but the diagnosis was significantly more common in males (odds ratio [OR],* 2.8). An ADHD diagnosis in either parent was strongly associated with the diagnosis in the child (OR, 3.5–4.2). Other mental illnesses, particularly mental retardation, pervasive developmental and mood disorders in mothers, but not in fathers, were also predictive of ADHD in the children.

Maternal use of bupropion (*Wellbutrin*) during pregnancy was associated with a significantly increased prevalence of ADHD in the offspring: 4% of all bupropion exposed children, compared with 2.5% of children exposed to an SSRI and 2.5% of those whose mother had depression but were not treated pharmacologically. After adjustment for
confounding factors, the OR for development of ADHD by age 5 years in children of mothers who filled a bupropion prescription during pregnancy was 3.6 (p=0.02). Analysis of exposure timing showed bupropion use during the second trimester was responsible for increased risk (OR, 14.7). Maternal use of an SSRI or other antidepressant during pregnancy was not associated with ADHD in the offspring.

The observational nature of the study and use of claims data limit the conclusions that can be drawn from this research, and a causal relationship between bupropion use and ADHD cannot be confirmed. Another important limitation is the young age at which ADHD was diagnosed and/or treated in the sample. ADHD is typically diagnosed at an older age and thus the children identified before age 5 may represent the most severe cases or misdiagnosis of other disorders. In addition, maternal smoking, which is known to increase ADHD risk and may have been a factor in the choice of bupropion treatment, was not systematically evaluated. However, given the large odds ratio associated with second trimester exposure, the possible causal relationship between ADHD and fetal bupropion exposure should be further evaluated.

Figueroa R: Use of antidepressants during pregnancy and risk of attention-deficit/hyperactivity disorder in the offspring. *Journal of Developmental and Behavioral Pediatrics* 2010; doi: 10.1097/DBP.0b013e3181e5ac93. From Mount Sinai School of Medicine, New York, N.Y.; and Carnegie Mellon University, Pittsburgh, Penn. Source of funding not stated. The author did not include a statement disclosing potential conflicts of interest.

*See Reference Guide.

### Second-Generation Antipsychotics Compared

Second-generation antipsychotics differ little in efficacy and are generally not more effective than first-generation agents, according to a comprehensive review of their use in children and adolescents with psychotic and bipolar spectrum disorders. The main differences among the second-generation drugs are in the rates and severity of adverse effects, particularly weight gain.

**Methods:** The authors identified all comparative studies of second-generation antipsychotics in children and adolescents published since 1990. The analysis was restricted to studies of patients with psychosis and bipolar spectrum disorder. The 34 studies, with a total of 2719 patients, included 23 comparisons of different agents, 9 placebo-controlled studies, and 2 studies comparing a second-generation drug to a first-generation one. Half of the studies were randomized controlled trials. The sample also included non-randomized and naturalistic studies and retrospective chart reviews. Most of the studies lasted 3 months or less.

**Results:** Second-generation antipsychotics were superior to placebo, but there were no significant differences in overall efficacy between the second-generation drugs or between second- and first-generation agents. The single exception was superior efficacy of clozapine, compared with haloperidol and olanzapine, in refractory schizophrenia.

The investigators compared 3 types of adverse effects: metabolic, prolactin-related, and neuro-motor. Mean weight gain was greater with olanzapine than other agents, ranging from about 8 to 35 lbs. Second-generation antipsychotics generally caused greater weight gain than older agents, though there were no direct comparisons with aripiprazole and ziprasidone, the second-generation drugs that cause the least amount of weight gain.

Increase in prolactin levels was greater in patients taking risperidone (average 8.3–49.6 ng/ml) than olanzapine. Aripiprazole was associated with decreases in prolactin, while other second-generation agents had mostly neutral effects. Second-generation agents had generally similar neuromotor adverse effects and were associated with less parkinsonism and akathisia than older agents.
Discussion: This review confirms that second-generation antipsychotics are not a homogeneous drug class, but differ substantially in their adverse effects. Younger patients are not only more vulnerable to adverse effects of these drugs, but may also be more sensitive to their negative impact on body image and self-esteem. Monitoring the cardiovascular risks of weight gain and strategies to reduce this risk have received little attention in children and adolescents. The authors recommend using lower-risk agents earlier in treatment, replacing them with higher-risk drugs only if necessary.


*Drug Trade Names: aripiprazole—Abilify; haloperidol—Haldol; clozapine—Clozaril; olanzapine—Zyprexa; risperidone—Risperdal; ziprasidone—Geodon*

**Ultra-Brief Pulse ECT for Catatonia**

Electroconvulsive therapy has been shown to be safe and effective in children and adolescents with serious mental illness, but cognitive impairments and transient memory loss can occur. Recent research suggests shortening the pulse width of the electrical stimulus and adjusting the electrode placement can mitigate some of these effects. This improved right unilateral ultra-brief width protocol has not been systematically studied in young patients with catatonic features.

A 14-year-old female presented to the emergency department with a 1-month history of behavioral changes, declining appetite, depressed mood, social withdrawal, slowed movements and speech latency, and recent onset hallucinations. She was hospitalized with a first episode of major depression with psychotic and catatonic features. On admission she displayed waxy flexibility, staring, mutism, and rigidity and required assistance with most activities. She was treated with lorazepam, citalopram, and aripiprazole with limited improvement.

After nearly 2 weeks, ECT was started using the right unilateral ultra-brief pulse width (0.25 ms; traditional brief-pulses range from 0.5 to 1.5 ms) technique. With the first treatment, the patient experienced improvements in mood and appetite, but they waned over the following day. After 3 treatments, she reported no depressed mood and cessation of hallucinations and delusions, but mild cogwheeling rigidity developed and required benztrapine treatment. Social interactions improved after 5 treatments, and speed of movement increased after 7 sessions. After a total of 12 ECT sessions the patient returned to premorbid functioning and was discharged. There was no evidence of cognitive slowing or memory impairment. Symptoms remained in remission during 4 months of follow-up.

Rhoads J, Votolato N, Young J, Gilchrist R: The successful use of right unilateral ultra-brief pulse electroconvulsive therapy in an adolescent with catatonia. *Brain Stimulation* 2010; 3 (July):51–53. From Ohio State University, Columbus. The authors did not disclose potential conflicts of interest.

*Drug Trade Names: aripiprazole—Abilify; benztropine—Cogentin; citalopram—Celexa; lorazepam—Ativan*

**Fatty Acids and Depression**

A cross-sectional population-based study found an inverse relationship between high intake of fish and other dietary sources of fatty acids and depression among male, but not female, adolescents.

*Methods: Diet history and lifestyle questionnaires as well as a self-report depression measure were distributed to all students (n=12,451) at 25 junior high schools in Okinawa, Japan. Based on their dietary responses, the 6517 evaluable students were stratified into quintiles of fatty*
Depression was considered present if the adolescent’s score on the Center for Epidemiologic Studies Depression (CES-D) scale was ≥16 (maximum score, 60).

**Results:** Depressive symptoms affected 23% of male adolescents and 31% of females. After adjustment for potential confounding factors, a significantly lower incidence of depression was found among adolescent males with higher levels of fish consumption (odds ratio,* 0.73 for quintile 5; p=0.04 for the trend). Findings were similar when intake of docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and their combination were evaluated separately: odds ratios ranged from 0.71 to 0.79 among males with the highest level of dietary intake. No associations were found in female students.

**Discussion:** Although frequently studied in adults (with mixed results), this appears to be the first study to find an independent association between fish, EPA, and DHA intake and depression in an adolescent population. It is unclear why the association applied only to male adolescents, but females may require lesser intake of essential fatty acids and may retain them in body tissue more effectively than males. The authors caution that because lifestyle factors differ substantially in other parts of the world, these results apply only to Japanese adolescents and the findings cannot be extrapolated to other populations.

Murakami K, Miyake Y, Sasaki S, Tanaka K, et al: Fish and n-3 polyunsaturated fatty acid intake and depressive symptoms: Ryukyus child health study. *Pediatrics* 2010; doi 10.1542/peds.2009-3277. From the University of Tokyo, Japan; and other institutions. Funded by the Japanese Ministry of Health, Labor, and Welfare. The authors disclosed no financial relationships relative to this research.

---

**Reference Guide**

**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.

---

As a subscriber, you are entitled to a special discount on *Psychiatry Drug Alerts*. Order a 1-year trial subscription for only $79.00—that’s a $10 savings off the regular subscription price! Call us at **1-800-875-0058** for more information.

---

**Contributing Editor:** Bennett Silver, MD  
**Consulting Editor:** Theodore A. Petti, MD, UMDNJ–Robert Wood Johnson Medical School  
**Executive Editor:** Michael J. Powers  
**Associate Editors:** Trish Elliott, Tara Hausmann  
**Assistant Editors:** Mandie Stahl, Krista Strobel

---

**Statement of Editorial Policy:** All of the information and opinions presented in each *Child & Adolescent Psychiatry Alerts* article are strictly those contained in the cited article unless otherwise noted. Reader comments are welcome by mail, by telephone (800-875-0058) 8:30–4:00 Eastern time Monday–Friday, or by e-mail (child@alertpubs.com).

**Off-Label Drug Use Statement:** Some drugs discussed for specific indications in *Child & Adolescent Psychiatry Alerts* articles may not be approved for labeling and advertising for those indications by the United States Food and Drug Administration.