Fatty Acids Improved Autism

A pilot study\(^1\) supports results of previous research\(^2\) that showed omega-3 fatty acids benefitted male children with autism spectrum disorders.

**Methods:** Study participants (n=10) with diagnosed autism spectrum disorders received open-label omega-3 fatty acid supplements for 12 weeks. Capsules, administered twice daily, contained 190 mg eicosapentaenoic acid and 90 mg docosahexaenoic acid. Patients were evaluated at baseline and again at 6 and 12 weeks using the Autism Treatment Evaluation Checklist (ATEC) and other validated symptom measures.

**Results:** Nine patients completed the study; 1 withdrew for reasons unrelated to treatment. Of the 9 patients, ATEC scores improved in 8 by an average of 33%. Secondary outcomes showed a similar pattern. Most improvement occurred during the first 6 weeks of treatment. Some improvement was seen in core symptoms of autism such as speech and sociability. The final child did not respond, but showed no worsening. After 6 weeks, 1 patient stopped taking the supplements and his condition deteriorated.

**Discussion:** Adult studies for various indications have shown a dose-response curve associated with fatty acid treatment with lesser improvement at higher dosages. The optimal dose has not been determined.

\(^1\)Meiri G, Bichovsky Y, Belmaker R: Omega 3 fatty acid treatment in autism. *Journal of Child and Adolescent Psychopharmacology* 2009;19 (August):449–451. From Soroka University Medical Center, Beersheba, Israel. Source of funding not stated. The authors disclosed no commercial relationships that might pose conflicts of interest.


Aripiprazole Review

In pediatric patients, aripiprazole (*Abilify*) appears to offer some advantages over other atypical antipsychotics such as once daily dosing, lesser potential to induce hyperprolactinemia, a safer metabolic profile, and the lack of required cardiac monitoring. However, because there are few randomized controlled trials and little long-term safety data, the reviewers recommended aripiprazole as a second-line treatment option for limited indications.
Aripiprazole is sometimes called a third-generation antipsychotic because its mechanism of action differs from other atypicals. It variably regulates blockade of D2 and 5-HT1A receptors and also is active at other dopamine and serotonin receptors and in other neurotransmitter systems. Pharmacokinetics are similar in children and adults, but peak concentrations are higher and reached more rapidly in children. Gradual dose titration may minimize adverse effects in pediatric patients.

Four randomized placebo-controlled trials support the efficacy of aripiprazole for schizophrenia, bipolar type I disorder, and serious behavioral problems associated with autism. Open-label studies suggest efficacy for these and other indications including tic disorders, irritability and aggression, and ADHD. An open-label study recently found aripiprazole improved aggressive behavior in patients with conduct disorder (see next story). In bipolar disorder and schizophrenia, higher aripiprazole dosages (30 mg/day) results in a greater side effect burden than lower dosages (10 mg/day), without a clear advantage in efficacy. There are no dosing recommendations for tic disorders, irritability and aggression, ADHD, or other off-label uses.

Aripiprazole efficacy has not been compared head-to-head with other antipsychotics. However, its adverse effect profile may offer some advantages. It is not associated with weight gain, metabolic disturbances, hyperprolactinemia, or cardiac conduction abnormalities. ECG monitoring is not required; however, metabolic parameters should be monitored. Once-daily dosing is an option because of its long half-life. Aripiprazole is associated with sedation and somnolence, which can be useful with bedtime administration. Other adverse effects include extrapyramidal symptoms and akathisia, nausea, vomiting, GI upset, and headache; all are generally mild-to-moderate and can be minimized with gradual dose titration. In adults, aripiprazole has been associated with rare cases of tardive dyskinesia and neuroleptic malignant syndrome.

Aripiprazole has been approved for adult use by Health Canada, but there are no atypical antipsychotics approved for pediatric use in Canada. In the U.S., aripiprazole is approved specifically for bipolar I disorder in children aged 10–17 years and for schizophrenia in those aged 13–17 years.


**Aripiprazole for Conduct Disorder**

In an open-label study, aripiprazole (Abilify) was associated with improvements in aggressive behavior in children and adolescents with conduct disorder, once a tolerable starting dose was established.

**Methods:** Study subjects were 12 children (6–12 years) and 11 adolescents (13–17 years) with a primary diagnosis of conduct disorder and at least mildly aggressive behavior. Initial aripiprazole starting doses of 0.2 mg/kg were associated with vomiting and sedation in 4 of the first 5 patients, and the dose was approximately halved for all patients. Patients weighing less than 55 lbs received 1 mg/day, those weighing 55–110 lbs received 2 mg/day, those weighing 111–154 lbs received 5 mg/day, and all patients over 154 lbs received 10 mg/day. Twenty-four hour pharmacokinetics were assessed on days 1 and 14 of aripiprazole administration and then patients entered a 36-month safety extension study. All 23 patients completed the initial pharmacokinetic phase and entered the extension study. Aggression was measured using the 5-point Rating of Aggression Against People and/or Property (RAAPP) scale.

**Results:** Aripiprazole pharmacokinetics were similar in children and adolescents and were linearly proportional to the administered dose. Steady state was achieved by day 14. Five patients completed the planned 36 months of observation. The mean duration of aripiprazole
exposure was about 13 months. About two-thirds of patients received a dosage increase at the investigator's discretion. RAAPP scale scores decreased by an average of about 1 point by day 14, and improvements were maintained during extended treatment. Median Clinical Global Impression scores for symptom severity decreased from "moderately ill" at baseline to "borderline ill" at month 36. Neuropsychological tests showed minor improvement in cognitive function.

Following dosage adjustment, aripiprazole was generally well tolerated. Side effects were similar in children and adolescents. Nausea and somnolence were the most frequent complaints during initiation of therapy. There were no serious adverse events and no discontinuations for adverse events. Five patients had extrapyramidal symptoms, which were mild and resolved spontaneously or with dose reduction. No patient had an elevated prolactin level. On average, patients gained weight and body mass index increased by 1.8 in children and by 3.4 in adolescents, but weight gain is expected in this population.

Findling R, Kauffman R, Sallee F, Salazar D, et al: An open-label study of aripiprazole: pharmacokinetics, tolerability, and effectiveness in children and adolescents with conduct disorder. *Journal of Child and Adolescent Psychopharmacology* 2009;19 (August):431–439. From University Hospitals Case Medical Center, Cleveland, Ohio; and other institutions including Bristol Myers-Squibb and Otsuka Pharmaceutical Co. The authors have disclosed commercial relationships that might pose conflicts of interest, and several are employed by the manufacturers of Abilify.

### Psychophysiology of Attachment Disruption

The consequences of severe attachment disruptions can be profound, but risk can be partially offset by creating a positive and stable caregiving environment. A review was undertaken to clarify the psychophysiological processes that might be useful measures of attachment disruption.

The attachment behavioral system is a self-regulatory system in which the child seeks an attachment figure when he or she feels insecure. One psychobiological theory suggests there are 3 hierarchical systems within the autonomic nervous system that engage successively when the individual is faced with challenges. When the attachment figure is unavailable, the child may develop alternative self-regulatory processes, which become maladaptive if the situation is prolonged. Some of these alternative processes can manifest as alterations in autonomic reactivity and HPA axis activity.

A study of foster children found signs of autonomic reactivity (e.g., respiratory sinus arrhythmia and heart rate) were blunted compared to controls, suggesting that the social engagement system may be less active in children with disrupted attachments. Another study found cortisol (a marker of chronic stress) was less variable in a group of children in foster care than in controls, possibly reflecting a pattern of abuse and neglect. In a randomized trial, an intervention with new foster parents to promote secure attachment resulted in higher cortisol levels in the children, compared with controls.

Integrative Therapy for Attachment and Behavior (ITAB) was developed to help create positive selective attachments in severely impaired children in group homes. Through ITAB, a therapist builds a therapeutic attachment with the child, trains the child in adaptive behaviors, and then tries to expand their attachment network to regular caregivers. In a controlled study, ITAB was used in children aged 10–17 years with disrupted attachment, profound intellectual impairment, and blindness or visual impairment. Autonomic nervous system regulation was improved during behavior modification sessions in children who received ITAB, but not in controls. This finding suggests some children become able to use another person as a support for the regulation of physiological reactivity.

Topiramate Improved Tics in TS

There are currently 2 medications, haloperidol and pimozide, FDA approved for treatment of Tourette syndrome, but both cause weight gain and have been associated with tardive dyskinesia. After a report of improved tics in 2 adults taking topiramate, a small manufacturer-sponsored controlled trial was undertaken to evaluate the efficacy and safety of topiramate in TS.

Methods: Participants (n=29) in the multicenter double-blind controlled trial had received a diagnosis of TS ≥3 months before entry and were at least moderately ill. All met minimum tic severity criteria. Patients taking >1 medication for tics or comorbid disorders were excluded. The mean age was 16.5 years (range, 7–65 years) and 26 patients were male. Comorbid disorders were common and included attention deficit with or without hyperactivity (n=10), obsessive compulsive disorder (n=6); and migraines (n=8). After a washout period, patients received randomized 50–200 mg/day topiramate or placebo for 70 days. The primary outcome measure was the Yale Global Tic Severity Scale (YGTSS).

Results: Twenty patients completed randomized treatment; 12 in the topiramate group and 8 in the placebo group. Reasons for discontinuation were lack of efficacy (1 topiramate, 4 placebo), adverse effects (1 in each group), and loss to follow-up (1 in each group). Mean YGTSS tic scores decreased from 27 to 12 in the topiramate group and from 29 to 23 in the placebo group (p=0.02). Both motor and phonic tic scores decreased, and tic severity scores were reduced by 65% with topiramate.

Adverse effects of topiramate were reported by 11 patients (73%). Headache and diarrhea each affected 3 patients, abdominal pain and drowsiness/hypersomnia were reported by 2 patients, and cognitive slowing and kidney stone each occurred in 1 patient. In the topiramate group, patients lost a mean of nearly 5 lbs, while those in the placebo group gained about 4 lbs.

Discussion: Topiramate appears to have some advantages over the currently approved medications for TS because it does not cause the weight gain or tardive dyskinesia that limit their use. These preliminary results suggest topiramate may be effective at reducing tics and further study appears to be warranted. The study authors caution that because the treatment duration was short some adverse effects previously associated with topiramate may not have been detected.

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


Drug Trade Names: haloperidol—Haldol; pimozide—Orap; topiramate—Topamax

*Reference Guide Item.

Trends in Antipsychotic Prescribing

Using retail pharmacy data and a prescription and diagnosis database, investigators tracked changes in second-generation antipsychotic use between 2004 and 2008. In the population overall, second-generation antipsychotic use increased 33% (from 6.9 million prescriptions/year to 9.2 million) over the study period. Use in pediatric patients increased, but to a smaller degree: a 24% increase from 1 to 1.2 million prescriptions/year. The most common indication
for use was bipolar disorder (34%), followed by hyperkinetic syndrome, generally viewed as the ICD-10 equivalent of combined type ADHD (12%), pervasive developmental disorders (10%), emotional disorder of children/adolescents (10%), conduct disturbance (7%), and schizophrenia (3%). The reasons for use did not change during the study years.

In an expert commentary, Robert Findling, MD from Case Western Reserve University suggests the increase in antipsychotic use likely results at least in part from the growing evidence base supporting their efficacy in young patients. Limitations of these data include the reliability of the diagnostic data, lack of patient treatment history (i.e., was the antipsychotic first- or second-line treatment), and the accuracy of the bipolar diagnosis. However, this information combined with a thorough investigation of treatment outcomes and drug-associated risks could help prescribers, patients, and families make educated choices about antipsychotic treatment.

Cascade E, Kalali A, Findling R: Use of antipsychotics in children. Psychiatry (Edgemont) 2009;6 (June):21–24. From Quintiles, Inc., a contract research company; and the University of California, San Diego. Source of funding not stated. Two study authors are employed by Quintiles; and R. Findling has disclosed commercial relationships that might pose conflicts of interest.

**Antipsychotics and Prolactin Elevation**

In pediatric patients, the incidence of antipsychotic-induced hyperprolactinemia appears to vary widely by agent, ranging from 12% with quetiapine to 90% with haloperidol.

**Methods:** Published reports of antipsychotic-induced hyperprolactinemia in children (<12 years) and adolescents (12–18 years) were identified by literature search. All studies lasting >3 weeks were included in a systematic review. The 29 studies included risperidone; olanzapine; quetiapine; haloperidol; pimozide; clozapine; and ziprasidone. Seventeen of the studies had an open-label design, 4 were observational studies, and 8 were double-blind randomized trials.

**Results:** Risperidone was evaluated in 1390 patients. In short-term studies (mean duration, 5 weeks) prolactin levels increased from a pooled baseline mean of 7.9 ng/mL to 27.6 ng/mL. Levels decreased somewhat with longer treatment to a mean of 17.7 ng/mL in 1-year studies and to 24.9 ng/mL in 2-year studies. A total of 62% of study subjects had hyperprolactinemia (based on the individual studies’ reference ranges). Olanzapine, studied in 170 patients (weighted average duration of treatment, 28 weeks), increased the average prolactin level from 11.1 ng/mL to 24.2 ng/mL, and 31% of patients met criteria for hyperprolactinemia. Haloperidol, evaluated in 56 patients after 6–8 weeks, increased the average prolactin level from 7.7 to 29.1 ng/mL, and 90% of patients had hyperprolactinemia. With pimozide (n=46) levels increased from 12.4 to 24.5 ng/mL but the incidence of hyperprolactinemia was not reported. Clozapine, ziprasidone, and quetiapine did not appear to significantly increase prolactin, but data on these drugs was limited to small numbers of patients.

The most common clinical effects of hyperprolactinemia were gynecomastia and irregular menses. Only 2 studies of more than 1 year’s duration examined the relationship of an atypical (i.e., risperidone) to the progression of puberty, finding no effect. No study examined the effects of these agents on bone mineral density.

**Discussion:** Data on antipsychotic-induced hyperprolactinemia are limited and of mixed quality. Risperidone is the only drug with long-term follow-up. Some studies did not obtain baseline prolactin measurements, permitted the use of other prolactin-elevating drugs, or did not ascertain side effects systematically. Nevertheless, these observations suggest a cautious approach in children and adolescents, who may be more vulnerable than adults to the effects of hyperprolactinemia on sexual development and bone mineral density. Prolactin-related side effects of antipsychotic therapy should be evaluated systematically.
Prolactin levels should be measured in patients with sexual dysfunction, gynecomastia, galactorrhea, or hypogonadotrophic hypogonadism. Hyperprolactinemia can be treated by lowering the antipsychotic dose, switching to a prolactin-sparing drug, or adding a dopamine antagonist.


*Drug Trade Names:* clozapine—*Clozaril*; haloperidol—*Haldol*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; pimozide—*Orap*; risperidone—*Risperdal*; ziprasidone—*Geodon*

## Intuniv Approved for ADHD

Extended-release guanfacine (*Intuniv*) has received FDA approval for treatment of ADHD in patients aged 6–17 years.\(^1\) *Intuniv* is not a scheduled drug and has shown no potential for abuse or dependence. Randomized treatment with *Intuniv* significantly reduced ADHD symptoms in clinical trials,\(^2,3\) and adverse effects were generally mild. However, hypotension, bradycardia, and syncope did occur in some patients and *Intuniv* should be used cautiously in patients predisposed to these conditions, including those taking antihypertensives. Heart rate and blood pressure should be evaluated before starting *Intuniv* and then monitored periodically throughout treatment. *Intuniv* will be available in 1, 2, 3, and 4 mg strengths and is expected to be available in pharmacies in November 2009.


## Reference Guide

**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.