Autism Spectrum and Prenatal SSRI Exposure

Prenatal exposure to SSRIs was associated with increased risk of autism spectrum disorders (ASDs) in a study based on a large claims database. The association was modest, and the authors conclude that SSRI exposure is not a major risk factor for ASDs.

**Methods:** Using data from the Kaiser Permanente Medical Care Program in Northern California, children born between 1995 and 1999 and subsequently given a diagnosis of autism, Asperger syndrome, or pervasive developmental disorder not otherwise specified were identified. Each child was matched with 5 controls of the same age, gender, and birth hospital. Maternal antidepressant exposure was identified beginning 3 months before conception and for each pregnancy trimester. To investigate whether maternal psychiatric conditions confounded any relationship between antidepressants and ASDs, maternal mental health diagnoses were included in a multivariate analysis.

**Results:** The study population included 298 children with ASDs and 1507 control children. Twenty case mothers (6.7%) and 50 control mothers (3.3%) had at least 1 antidepressant prescription during the year before delivery. Because the majority of women were prescribed SSRIs, further analysis was limited to these agents. Women prescribed an SSRI during the year prior to delivery were twice as likely to have a child later diagnosed with an ASD than those not prescribed an SSRI (odds ratio,* 2.2; 95% confidence interval,* 1.2–4.3). The association was statistically significant for the preconception period and the first trimester but did not reach significance in the later trimesters, perhaps because there were few new SSRI prescriptions during these periods.

After adjustment for maternal psychiatric diagnosis, the association of first-trimester SSRI use with ASDs remained significant. ASDs were not associated with the indication for maternal SSRI treatment. In an analysis restricted to women who had a mental health diagnosis in the year before delivery (25 cases and 99 controls), risk of ASD was still elevated (odds ratio, 1.6), but the association was not statistically significant.
**Discussion:** These results indicate that SSRI exposure during pregnancy is associated with a modest increase in risk for ASDs, accounting for <3% of all cases in this patient population. Because this appears to be the first study of its kind, the conclusions must be considered preliminary and applied with caution. The small increase in risk of ASDs with prenatal SSRI exposure must be weighed against the dangers of untreated maternal depression.

Croen L, Grether J, Yoshida C, Odouli R, et al: Antidepressant use during pregnancy and childhood autism spectrum disorders. *Archives of General Psychiatry* 2011; doi 10.1001/archgenpsychiatry.2011.73. From Kaiser Permanente Northern California, Oakland; and other institutions. Funded by Kaiser Permanente; the Centers for Disease Control and Prevention; and other sources. The authors did not include disclosure of potential conflicts of interest.

*See Reference Guide.

### Adjunctive Olanzapine for Anorexia Nervosa

Adding olanzapine (*Zyprexa*) to standard management of anorexia nervosa did not produce additional weight gain or improve other outcomes in a small group of patients with the restricting subtype of the disorder.

**Background:** Two previous studies have investigated olanzapine in anorexia nervosa. Both were conducted in adults; 1 showed an effect on weight gain and 1 did not. The present study was undertaken to evaluate weight gain, metabolic profiles, and body image in younger patients.

**Methods:** Female patients receiving treatment at a single eating disorders clinic over a 4-year period were invited to participate in the pilot study. Of 94 eligible participants, 74 declined study participation because they did not want to gain weight or wanted to gain without the use of medication. The 20 patients, aged 12–21 years (mean, 17 years), who entered the study received individualized medical care, nutritional management, and psychological therapies, with treatment intensity adjusted as weight goals were met. In addition, they were randomized to receive 10 weeks of adjunctive treatment with either olanzapine (target dosage, 10 mg/day) or placebo.

**Results:** The mean baseline body mass index (BMI) was 16.4. Patients in both groups gained weight during the trial but were still underweight (mean BMI, 18) and hypometabolic at study end. Adding olanzapine to treatment did not result in greater weight or BMI increases. There was a trend toward increased fasting glucose at week 10 in the olanzapine group, but the difference from baseline was not significant. Insulin levels increased significantly from baseline with olanzapine (p=0.009). Neither measures of energy expenditure and substrate utilization nor cardiac function differed between the olanzapine and placebo groups. Olanzapine had no effect on general psychopathology or body image.

**Discussion:** In other patient populations, olanzapine-associated weight gain is partly explained by decreased resting energy expenditure and altered metabolism of carbohydrate, fat, and protein as energy substrates. The present findings do not support an olanzapine-associated decrease in energy expenditure as a contributor to weight gain. The lack of benefit observed in these patients, together with the high treatment refusal rate and the potential effects on insulin and glucose, suggest adjunctive olanzapine is not effective as a weight-promoting agent in adolescents with restricting-type anorexia nervosa.

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


*See Reference Guide.
Antipsychotics Compared in Early Onset Psychosis

Most studies of first-episode psychosis have reported outcomes after ≤1 year of treatment and they seldom compared drugs. The present study evaluated the long-term efficacy and safety of first- and second-generation antipsychotics in children and adolescents with schizophrenia or schizoaffective disorder.

**Methods:** Records were reviewed for all children and adolescents with schizophrenia or schizoaffective disorder treated at a single psychiatric clinic in Italy between 1990 and 2005. Follow-up data spanning 3–11 years were available for 47 patients who were evaluated at frequent intervals with standardized rating instruments.

According to the institution’s protocol, patients who received a diagnosis before 1999 were first treated with haloperidol, with nonresponders switched to another first-generation agent and then to clozapine. When risperidone and olanzapine were introduced in the mid-1990s, they replaced the second conventional antipsychotic. After 1999, all patients were started on a second-generation drug, usually risperidone. An incomplete response or intolerance resulted in a switch to another second-generation agent or haloperidol. Clozapine was typically used after failure of at least 2 other agents. Aripiprazole and quetiapine were introduced later in the observational period and used in relatively few patients.

**Results:** A total of 47 patients were available for follow-up at 3 years and 41 were available at 5 years. Positive response was defined as a ≥20% reduction in Positive and Negative Syndrome Scale (PANSS) score, with no positive symptom rated as more severe than "mild" and a Clinical Global Impression Improvement (CGI-I) rating of "much improved" or "very much improved." Clozapine had the highest overall response rate: of 25 patients ever treated with the agent, 19 (76%) had a positive response at 5 years. (See table for 3- and 5-year response rates for all agents.)

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<th>Antipsychotic response rates at 3 and 5 years</th>
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<td><strong>Haloperidol</strong></td>
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<td><strong>Risperidone</strong></td>
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<td><strong>Olanzapine</strong></td>
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<td><strong>Quetiapine</strong></td>
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<td><strong>Clozapine</strong></td>
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Sufficient data were available for 4 pairwise comparisons of drugs used in the same subjects at different times: haloperidol vs risperidone; haloperidol vs clozapine; risperidone vs clozapine; and olanzapine vs clozapine. The analysis found that both risperidone and clozapine were significantly superior to haloperidol at reducing total PANSS score. Clozapine also produced significantly greater improvement than risperidone and olanzapine on this measure.

A single patient discontinued clozapine for lack of efficacy, in contrast to 43–67% for the other second-generation agents and 96% for haloperidol. Treatment withdrawal for adverse effects was more common with risperidone and olanzapine than with the other agents. Clozapine was withdrawn in 3 patients because of neutropenia. However, it was well tolerated in those who continued to take it for 3–11 years. Excessive weight gain was most common
with olanzapine (60%) but also occurred frequently with clozapine and risperidone. The authors conclude that clozapine is effective and may be underused in children and adolescents with early-onset psychosis that is not responsive to other antipsychotics.

Cianchetti C, Ledda M: Effectiveness and safety of antipsychotics in early onset psychoses: a long-term comparison. Psychiatry Research 2011; doi 10.1016/j.psychres.2011.03.020. From the Hospital-University of Cagliari, Italy. The authors declared no conflicts of interest.

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

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**Self-Embedding Behavior: Extreme Form of Self-Injury**

Pediatric self-embedding behavior (SEB) is an extreme form of self-injury, involving the insertion of objects into the soft tissue, either under the skin or into muscle, and occurring mostly in teenage girls with bipolar disorder. Few cases of SEB have been described in the pediatric literature; those that have been published involved adolescents with developmental delays. A retrospective chart review was undertaken to characterize the disorder because it is associated with suicide risk and requires urgent assessment and treatment.

This report is based on 3 years of experience. Between 2005 and 2008, 600 patients underwent interventional radiologic treatment at an urban pediatric hospital for foreign bodies embedded in soft tissue. Most patients presented to the emergency department for evaluation of related pain or infection, and the foreign body was removed under radiologic guidance. Other reasons for seeking emergency care were the patient’s admission of self-embedding objects or reports from others who had observed the behavior. Most foreign bodies were the result of accidental injury; however, the insertion was intentional and self-inflicted in 11 patients.

Of the 11 patients, aged 14–18 years (mean, 16 years), 9 were female. All of the patients had previous (often multiple) psychiatric diagnoses: bipolar disorder (100%); posttraumatic stress disorder (64%); depression (45%); borderline tendencies (45%); ADHD (36%); conduct disorder (18%); and panic disorder, obsessive-compulsive disorder, and overanxious disorder (9% each). Nearly all patients (10 of 11) had a history of out-of-home placement and were living in a group home or psychiatric facility while they engaged in SEB. Patients had a mean of 1.9 prior episodes of SEB, with a mean duration of 63 days between episodes. The most common reported purpose of SEB was suicidal ideation, present in 6 of 8 patients for whom a reason was recorded.

Patients embedded a mean number of 2.4 objects in a single episode (range, 1–11). Inserted objects were metal, glass, graphite, wood, plastic, and crayon. Most patients embedded objects in their arm; other sites were the neck, foot or ankle, and hand.

With this report, the authors hope to begin to develop a clinical profile of adolescents with this virtually undocumented disorder. SEB differs in intent from other forms of self-injury. SEB is intended to cause serious harm or induce death. In contrast, nonsuicidal self-injury is undertaken to induce positive feelings or seek help.

Management of SEB should involve a multispecialty team of primary care and emergency physicians, interventional radiologists, and behavioral health specialists. Treatment must immediately interrupt the cycle of self-harm and involve subsequent removal of the foreign bodies and address the patient’s need for mental-health care.

Proposed DSM-5 criteria for autism spectrum disorder (ASD) are not sensitive enough to identify many children who receive a diagnosis using current criteria, according to an epidemiologic study. Without modification, the newer criteria could result in a loss of access to needed services.

Methods: Investigators screened all 8-year-old children living in 1 health district in Finland using the Autism Spectrum Screening Questionnaire (ASSQ). Children with parent-reported mental retardation were not screened but did receive other evaluations. Of 4414 children screened, 73 scored positive on the ASSQ, based on threshold parent and/or teacher ratings. These children underwent diagnostic evaluation, as did 52 others who had relatively high scores that did not meet the threshold. Diagnostic evaluations were performed using the Autism Diagnostic Interview–Revised (ADI-R), the Autism Diagnostic Observation Schedule (ADOS) module 3, an IQ test, and, when needed, direct classroom observation. ASDs were diagnosed by clinical consensus, based on DSM-IV-TR criteria. The results were then compared with DSM-5 draft criteria posted by the American Psychiatric Association in February 2010.

Results: The prevalence of ASD in this population was 8.4 per 1000 using the DSM-IV-TR criteria; 65% of the children were considered high-functioning (IQ, ≥70). Autism was diagnosed in 4.1 children per 1000. Of the 26 children with IQ of ≥50 who were diagnosed as having ASD in the study, only 13 had registered ASD diagnoses in their medical records. Of 12 children with a full-scale IQ of <50, 9 had a recorded diagnosis of ASD. Clinical observation indicated that an additional 7 children had ASD features that could not be identified with any of the diagnostic criteria sets. If these cases were identified as pervasive developmental disorder not otherwise specified, the total prevalence of ASD in this population would be 10/1000 children.

Application of the DSM-5 draft criteria identified only 12 of the 26 children (46%) with an IQ ≥50 identified as having ASD by the DSM-IV-TR criteria. The draft criteria did not identify any of the 11 children with Asperger syndrome or 3 high-functioning autistic children.

Discussion: The prevalence of DSM-IV-TR autism spectrum disorder in the Finnish cohort is comparable to epidemiologic studies in other populations. The authors proposed several modifications to the criteria that would have increased their diagnostic sensitivity to 96% by DSM-IV-TR criteria. These modifications include

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### Autism Spectrum Disorder: DSM-5 Draft for Pervasive Developmental Disorders Posted by the American Psychiatry Association February 2010

Autism Spectrum Disorder must meet criteria 1, 2, and 3:

1. Clinically significant, persistent deficits in social communication and interactions, as manifest by all of the following:
   a. Marked deficits in nonverbal and verbal communication used for social interaction
   b. Lack of social reciprocity
   c. Failure to develop and maintain peer relationships appropriate to developmental level

2. Restricted, repetitive patterns of behavior, interests, and activities, as manifested by at least TWO of the following:
   a. Stereotyped motor or verbal behaviors, or unusual sensory behaviors
   b. Excessive adherence to routines and ritualized patterns of behavior
   c. Restricted, fixated interests

3. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities).
more liberal classification of communication deficits, social relationships, routines and rituals, and idiosyncratic sensory behavior. Importantly, they recommend less emphasis on symptom presentation in early childhood, which would exclude many children with Asperger syndrome. The authors suggest dividing ASD into 2 categories, a severe and a milder form.

Mattila M-L, Kielinen M, Linna S-L, Jussila K, et al: Autism spectrum disorders according to DSM-IV-TR and comparison with DSM-5 draft criteria: an epidemiological study. *Journal of the American Academy of Child and Adolescent Psychiatry* 2011;50 (June):583–592. From the University Hospital of Oulu, Finland; and other institutions. *Funded by Finland's Slot Machine Association; and other institutions. The authors disclosed no potential conflicts of interest.*

**Valproate and Cognitive Development in Offspring**

Children exposed in utero to valproate and related products have a greater risk of scoring low on cognitive tests than children exposed to other anticonvulsants. The FDA has issued a warning for healthcare professionals about the increased risk as well as a reminder about other major malformations, including neural tube defects, that have been associated with gestational valproate use. Benefits of maternal treatment should be weighed against fetal risk, and alternate medication with less risk for adverse birth outcomes should be considered.


**Reference Guide**

**Confidence Interval:** The range in which the value of a variable in question is likely to fall, usually calculated at 95%. Confidence intervals indicate the reliability of an estimate, and a very wide interval may indicate that more data should be collected before making definite conclusions.

**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.