Increased Diabetes Risk with Antipsychotics

In a retrospective cohort study, children and adolescents who received antipsychotics had a 3-fold increase in risk of type 2 diabetes, compared with their peers who received other psychotropic drugs.

Methods: The analysis included patients, aged 6–24 years (the upper age limit corresponds to the World Health Organization's definition of youth), enrolled in the Tennessee Medicaid program for ≥1 year between 1996 and 2007. The sample included youths with no evidence of diabetes at baseline and, for the purpose of matching, excluded those with a mental illness for which antipsychotics were the only recommended treatment—e.g., schizophrenia, Tourette syndrome, and autism. Comparison subjects were young people who recently initiated use of other psychotropic drugs but had not taken an antipsychotic in the past year. Cases were propensity score-matched* to controls on 115 different variables, including psychiatric diagnosis and previous psychotropic medications.

Results: The sample included nearly 29,000 young people who took antipsychotics and nearly 14,500 controls, with a total of about 56,000 patient-years of follow-up. The majority of antipsychotic-exposed patients received atypical agents (87%), most often risperidone (37%), quetiapine (20%), and olanzapine (20%).

New-onset type 2 diabetes was evident in 106 patients. The incidence of type 2 diabetes was 3-fold higher in patients who received antipsychotics than those given a prescription for other drugs (hazard ratio,* 3.03). The risk elevation was statistically significant within the first year of treatment, increased as a function of cumulative antipsychotic dose, and remained significant for a year following discontinuation of the drug. When the cohort was restricted to patients aged 6–17 years, risk estimates were slightly higher. During follow-up, there were 21 new cases of type 1 diabetes. This disorder had no association with antipsychotic use.

Risk of type 2 diabetes was elevated with most of the individual atypical antipsychotics; adjusted hazard ratios ranged from 2.2 for risperidone and olanzapine to 7.7 for aripiprazole.
Additional analyses determined that type 2 diabetes was not diagnosed more frequently as a result of increased screening in patients who received antipsychotics.

**Discussion:** In this study cohort, there were an estimated 16 additional cases of type 2 diabetes per 10,000 patient-years of antipsychotic exposure, with a number needed to harm* of 633. The risk estimates from this study should be applied cautiously when prescribing, depending on the child’s age and body mass index.

Bobo W, Cooper W, Stein M, Olsson M, et al: Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. *JAMA Psychiatry* 2013; doi 10.1001/jamapsychiatry.2013.2053. From Vanderbilt University School of Medicine, Nashville, TN; and other institutions. **Funded by the Agency for Healthcare Research and Quality. Two study authors disclosed financial relationships with commercial sources.**

*Drug Trade Names:* olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal*

*See Reference Guide.

### Psychosocial Treatments for Bipolar Disorders

According to a comprehensive literature review, there are no well-established psychosocial treatments for pediatric bipolar spectrum disorders. However, there is useful evidence supporting several forms of therapy. Family psychoeducation plus skill building—ingredients that are common to these therapies—should be considered first-line treatment for pediatric bipolar disorders.

Evidence is strongest for and supports treatments that offer psychoeducation and skill building—specifically, single- or multi-family psychoeducation about mood symptoms, disease course, and treatment, and building skills for symptom management, adjunctive to treatment-as-usual or medication. These treatments are Multi-Family Psychoeducational Psychotherapy (MF-PEP), Family-Focused Treatment for Adolescents with Bipolar Spectrum Disorders (FFT-A), and FFT for high-risk youth (FFT-HR).

Evidence from less rigorous studies with relatively small sample sizes and with inconsistent blinding supports MF-PEP and Individual-Family Psychoeducational Psychotherapy (IF-PEP). Still less stringent evidence, generally from pilot studies, provides more support for MF-PEP and FFT-HR, as well as support for individual, family, or multi-family cognitive-behavioral therapy (CBT), dialectical behavior therapy (DBT), and social rhythm therapy.

The review authors concluded that treatments offering family psychoeducation plus skill building meet criteria for being "probably efficacious," and CBT is "possibly efficacious." They consider other treatments, including DBT, interpersonal therapy, and social rhythm therapy, to be "experimental." These results, although promising, are limited by the small amount of research, samples, and settings. However, the authors recommend that psychoeducation and skill building be incorporated into clinical practice. An important element is teaching the parents how to be effective advocates and coordinators of health care for their children.

Fristad M, MacPherson H: Evidence-based psychosocial treatments for child and adolescent bipolar spectrum disorders. *Journal of Clinical Child and Adolescent Psychology* 2013; doi 10.1080/15374416.2103.822309. From The Ohio State University, Columbus. **Funded by the NIMH. One study author disclosed financial relationships with commercial sources.**

### One-Session Treatment for Specific Phobias

According to a literature review, considerable evidence supports one-session therapy (OST) for specific phobias in children and adolescents.

One-session therapy is an exposure-based therapy that typically lasts 2.5–3 hours. Originally developed decades ago to treat spider phobia in adults, OST has been successfully adapted over the last 15 years for use in adolescents and children as young as age 7 years. About a week
before the single session, the therapist meets with the child to assess the problem, establish rapport, and develop a plan. The treatment then comprises a series of exposures used to test the child’s catastrophic beliefs and distorted expectations about the stimulus. Common cognitive-behavioral techniques—i.e., participant modeling; reinforcement; psychoeducation; skills training; and cognitive challenges—are incorporated into treatment.

A total of 8 published studies have investigated OST.

- The first 2 studies found OST superior to eye movement desensitization and reprocessing (EMDR) in small samples of girls with spider phobia.
- In a randomized trial of 60 patients with various phobias, OST was equally effective with or without a parent present, and both variations of OST were superior to a wait-list control condition.
- In the largest trial, 196 children were randomly assigned to OST, psychoeducation without exposure, or a wait-list. Both active treatments were effective in reducing both phobia severity and the number of children who met diagnostic criteria. OST was superior to psychoeducation for some outcome measures.
- Another study found no difference between OST and psychoeducation, but in this case psychoeducation incorporated many of the same elements as OST.
- In 2 studies in a partially overlapping sample of girls with spider phobia, OST was superior to a wait-list control, and active treatment resulted in physiological benefits evident on electromyography and electroencephalography.
- In the final report, OST was used successfully in a boy with pervasive developmental disorder and specific phobias.

There appear to be no age or gender differences in responsiveness to OST. Research findings have shown carryover benefits to other comorbid phobias and anxiety disorders and increased levels of self-efficacy, mastery, and bravery. Studies with long-term follow-up showed lasting benefits.

Ollendick T, Davis III T: One-session treatment for specific phobias: a review of Öst's single-session exposure with children and adolescents. Cognitive-Behaviour Therapy 2013; doi 10.1080/16506073.2013.773062. From Virginia Polytechnic Institute and State University, Blacksburg; and Louisiana State University, Baton Rouge. Funded by the NIMH; and other sources. The authors declared no competing interests.

### Guanfacine: Morning vs. Evening Dosing

In a randomized, multicenter, placebo-controlled study, extended-release guanfacine (Intuniv) monotherapy was equally effective and well tolerated whether administered in the morning or in the evening.

**Background:** Sedation and somnolence are common adverse effects of guanfacine. Anecdotal reports have suggested that evening administration is sometimes recommended in an effort to alleviate these troublesome symptoms.

**Methods:** Study participants were children, aged 6–12 years, with a primary diagnosis of ADHD of the hyperactive-impulsive or combined subtype, with symptoms of at least moderate severity. Patients were randomly assigned to 1 of 3 treatments: guanfacine upon waking in the morning, plus an evening placebo at around 7 pm; evening guanfacine with a morning placebo; or morning and evening placebo. Dosing was optimized over 5 weeks, with an optimal dose defined as that producing a clinically significant reduction in ADHD symptoms, indicated by a ≥30% decrease in the ADHD Rating Scale-IV (ADHD-RS-IV) score, with an acceptable level of side effects. A 3-week dose maintenance period was followed by a 9-day drug taper. The primary efficacy measure was the ADHD-RS-IV.
Results: Data were available for 333 study patients who received ≥1 dose of study medication. The mean optimal dosage of guanfacine was 2.9 mg/day. Guanfacine was superior to placebo regardless of the time of administration. Patients exhibited a mean 20 point decrease in ADHD-RS-IV score with guanfacine administered at either time, compared with an 11-point decrease with placebo (p<0.001). The effect sizes* were nearly identical: 0.75 for morning dosing and 0.78 for evening dosing. Guanfacine produced significantly greater improvement than placebo on both the hyperactivity/impulsivity and inattention subscales of the ADHD-RS-IV. There were not significant differences on either subscale relative to morning versus evening guanfacine administration.

Three patients experienced severe adverse effects judged to be guanfacine-related. Two had mild-to-moderate syncope, and a third experienced suicidal ideation. In all 3 cases, treatment was tapered and the adverse effects resolved. Other treatment-emergent adverse events were those previously reported with guanfacine, and they occurred at similar rates in the groups taking guanfacine in the morning or evening. The predominant adverse effects, somnolence, sedation, and hypersomnia, generally resolved with continued treatment.

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

Integrated Behavior Therapy for Selective Mutism

A newly developed exposure-based intervention, Integrated Behavior Therapy for Selective Mutism (IBTSM), was effective in a preliminary randomized study.¹

Methods: The study enrolled children, aged 4–8 years, who were attending school or another structured daily group activity and who met DSM-IV criteria for selective mutism. The children were randomly assigned to receive IBTSM in 20 sessions over 24 weeks or to a 12-week wait list, followed by IBTSM. The therapy was administered according to a treatment manual,² and focused on gradual exposure to the feared stimuli/situation as the primary mechanism of symptom reduction. After 3 sessions of assessment and orientation with the parent and child, the therapist introduced behavioral exposure exercises during therapy and out-of-session assignments of gradually increasing difficulty. School behavioral tasks were developed jointly by the therapist and the child’s teacher. During the last several sessions, control of the child’s progress was transferred to the parent, and relapse prevention was discussed. Outcomes were rated at 24 weeks in the IBTSM group and at 12 weeks in the control group. Response was assessed by blinded, independent evaluators using the Clinical Global Impression-Improvement (CGI-I) scale.*

Results: Of 23 children who met eligibility criteria, 2 declined participation. The remaining 21 patients completed follow-up assessments, and all 12 children assigned to the IBTSM group completed the therapy. Patients had a mean age of 5 years, with an average age of selective-mutism onset of 3 years. Teachers rated each child’s baseline mutism at school as “moderately” to “extremely” interfering.

At the 24-week assessment, 9 children (75%) in the IBTSM group met response criteria (CGI-I score ≤2), compared with none of those in the wait-list condition (p=0.001). Of the treated children, 8 (67%) no longer met diagnostic criteria for selective mutism, while all wait-listed children still met criteria (p=0.002). Children who received IBTSM also showed
significant improvement in speaking behaviors and reductions in social anxiety, as rated by parents. Teachers reported increases in speaking behaviors and in the number of words spoken, but no significant changes in social anxiety in the children who received treatment. At 3-month follow-up, all but 1 of the children maintained their response.

**Discussion:** IBTSM was based on previously validated treatments for social anxiety, but incorporated adaptations to compensate for the relatively early age at onset of selective mutism, the failure of children to speak in early sessions, and the need to involve teachers extensively. The observation by teachers that therapy did not reduce social anxiety suggests that children may use speech avoidance to reduce social anxiety, and treating mutism may not affect anxiety or may even increase it.

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

*1Bergman R, Gonzalez A, Piacentini J, Keller M: Integrated behavior therapy for selective mutism: a randomized controlled pilot study. *Behaviour Research and Therapy* 2013;51:680–689. From the UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles; and private practice, Hayward, CA. Funded by the NIMH. The authors did not include disclosure of potential conflicts of interest.


*See Reference Guide.

### Computerized Decision Aid for ADHD Evaluation

Use of a computerized decision support module resulted in improved evaluation of ADHD in a randomized trial. The system is based on freely available open-source software and can be adopted easily and inexpensively.

**Methods:** The trial was conducted at 4 university-based, pediatric primary care practices, 2 of which were randomly selected to implement the program and 2 of which functioned as control sites. All 4 practices utilized a clinical decision support system called Child Health Improvement through Computer Automation (CHICA). The system includes a scannable form with 20 screening questions that parents complete in the waiting room. Based on this information, the physician is prompted by the system to ask additional questions. The "enhanced" ADHD module includes 3 ADHD-specific screening questions for parents of children aged 5–12 years. Positive answers prompt the system to print the Vanderbilt assessment scales, which are to be completed by both the parents and the child’s teacher. When complete, both forms are automatically scored by the system. The module also makes treatment recommendations based on the American Academy of Pediatrics’ guidelines for ADHD management.

Outcomes following use of the ADHD module were evaluated by comparing each practice’s adherence to clinical care guidelines. The primary outcome of interest was the proportion of patients who had a completed structured diagnostic assessment, defined as completed Vanderbilt forms by both the parent and teacher, before receiving the diagnosis of ADHD.

**Results:** The investigators reviewed the charts of 84 patients with a new diagnosis of ADHD, 42 each in the intervention and control groups. Before implementation of the ADHD module, 60% of patients in the intervention group and 50% of controls received a structured diagnostic assessment. After implementation, the proportion increased to 81% in the intervention group and decreased to 38% in controls. After adjustment for age, gender, race/ethnicity, and insurance status, the odds ratio* for receiving a structured diagnostic assessment in the intervention group was 8.0.

The study was not designed to detect changes in ADHD care, but results of a preliminary analysis suggests that the children in the intervention group were more likely to receive
reassessments of symptoms at the 3-month follow-up visit, mental health referrals, and visits to a mental health specialist. These differences, however, were not statistically significant.

Discussion: Evidence suggests the diagnosis and management of ADHD in primary care settings is suboptimal. This occurs in part because it is difficult for pediatricians to screen for every condition. An automated process can increase the evaluation rate and also the thoroughness of symptom ascertainment from parents and teachers.

Carroll A, Bauer N, Dugan T, Anand V, et al: Use of a computerized decision aid for ADHD diagnosis: a randomized controlled trial. Pediatrics 2013;132 (September):e623-e629. From Indiana University School of Medicine, Indianapolis; and other institutions. Funded by the NIH. The authors declared no conflicts of interest.

*See Reference Guide.

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Clinical Global Impression-Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

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.

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.

Number Needed to Harm (NNH): A measure of how many patients need to be exposed to a risk-factor to cause harm in 1 patient that would not otherwise have been harmed. Lower NNH indicates more attributable risk.

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.

Propensity Score Matching: Selection bias can be problematic when using observational data, making causal relationships difficult to establish. Propensity score matching is a correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

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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