Routine Screening for Suicide Risk

According to a recommendation statement from the U.S. Preventive Services Task Force, there is insufficient evidence to support routine screening of adolescents for suicide risk in primary care. There is also insufficient data on the benefit of interventions in patients identified by screening and on the potential harms of screening. They do recommend, however, that clinicians be aware of psychiatric problems in their patients and that those with problems be asked about suicidal ideation and referred for psychotherapy, pharmacotherapy, or case management. In addition, adolescents should be screened for depression when appropriate systems are in place for its diagnosis, treatment, and follow-up.


Day Treatment for Anorexia Nervosa

In a randomized trial in adolescent girls with anorexia nervosa, day treatment after brief inpatient stabilization was as effective for weight restoration as longer inpatient care.

Methods: This noninferiority trial* was conducted at 5 university hospitals and 1 major general hospital in Germany that offered specialist care for anorexia. Participants were 172 young women, aged 11–18 years (mean age, 15 years), scheduled for their first inpatient treatment of anorexia nervosa. All participants were hospitalized for 3 weeks, and then randomized to either day treatment or continued inpatient treatment. Treatment, based on weight restoration, nutritional counseling, cognitive-behavioral therapy, and family therapy, was of the same intensity in both groups and was provided by the same therapists. Discharge from randomized treatment was permitted when a patient had maintained their target weight for 2 weeks. Subjects were followed for 12 months. The primary study outcome was change from baseline in body mass index (BMI).
**Results:** The mean durations of treatment were 14.6 weeks in the inpatient group and 16.5 weeks in the day-treatment group. Day treatment was not less effective than inpatient treatment. Patients in both groups achieved substantial weight gain. Subjects’ mean BMI on admission was 15 kg/m². At the 12-month follow-up, mean BMI was 17.8 in the inpatient group, compared with 18.1 in the day-treatment group (mean difference, 0.46 kg/m²; p<0.0001). Day treatment was superior to inpatient treatment with regard to mental state and psychosexual adjustment, measured with the Morgan and Russell Average Outcome Score.

Costs of treatment were about 20% lower for step-down care than inpatient care (p=0.002). Similar numbers of patients in both groups had a serious adverse event between admission and the 12-month follow-up, including 3 instances of suicidal ideation in the inpatient group and 2 in the day-treatment group. About one-fourth of each group continued to meet diagnostic criteria for anorexia nervosa at 12 months. The rate of readmission for an eating disorder—25% in the young women who received inpatient treatment and 15% in those who received day treatment—did not differ significantly between the groups.

**Discussion:** The economic implications of this research are substantial given the high costs of treating anorexia. In addition to its lower costs, day treatment has other theoretical advantages. The skills learned might be more easily transferable to daily life; adolescents tend to experience hospitalization as coercive; and they may benefit from continued contact with their social networks.

Herpertz-Dahlmann B, Schwarte R, Krei M, Egberts K, et al: Day-patient treatment after short inpatient care versus continued inpatient treatment in adolescents with anorexia nervosa (ANDI): a multicentre, randomised, open-label, non-inferiority trial. Lancet 2014;383 (April):1222–1229. From the University Hospital of the RWTH Aachen, Germany; and other institutions. Funded by the German Ministry for Education and Research. Seven study authors disclosed financial relationships with commercial sources; the remaining 10 authors declared no conflicts of interest.

*See Reference Guide.

**Family-Based Treatment for Early Childhood OCD**

Modified family-based cognitive-behavioral therapy (CBT) was more effective than relaxation therapy in young children with obsessive-compulsive disorder in a randomized trial. This trial adds to the evidence base supporting CBT emphasizing exposure and response prevention (EX/RP) and extends downward the age range in which this treatment is useful.

**Methods:** Study participants (n=127) were children, aged 5–8 years (mean age, 7 years), with a primary diagnosis of OCD of at least moderate severity that had been clinically stable for ≥3 months. CBT was delivered in 12 sessions over 14 weeks; the first 2 were parent-only and the remaining sessions included both parent and child. The primary components were psychoeducation, behavior management skills training for the parents, EX/RP, and family process. The program was modified for families with young children, with increased parental involvement; developmentally tailored psychoeducation, exposures, and homework; and a greater focus on the family context. The comparison treatment was family-based relaxation therapy, delivered on the same schedule as CBT. The primary efficacy measures were the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and the Clinical Global Impression–Improvement (CGI-I) scale.* Response was defined as a CGI-I score of 1 or 2.

**Results:** At 14 weeks, response rates were 72% for CBT and 41% for relaxation training. The number needed to treat* for 1 additional response with CBT was 3.2, and the effect size* for the superiority of CBT measured by CY-BOCS improvement was 0.84.

The mean number of completed sessions was 11.2 (out of 12) for CBT and 10.1 for relaxation training. Families that received relaxation training were more likely to drop out of therapy and seek alternative treatments than those that received CBT.
Discussion: These results are consistent with previous trials of CBT in older children and an earlier pilot study of the modified treatment in young children. The results are particularly notable given the use of a comparison treatment with face validity, similar credibility, and the same amount of time with the therapist. The results lend support to the belief that children as young as 5 years can have real and disabling OCD that warrants active treatment, not a watch-and-wait approach.

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


*See Reference Guide.

Maternal Smoking and ADHD-Like Neural Alterations

Young adults who were prenatally exposed to tobacco smoke exhibited neural alterations similar to those seen in ADHD.

Methods: Testing was carried out in 175 participants who were part of an ongoing German study of the long-term outcome of early-life risk factors. Maternal smoking had been assessed by questionnaire 3 months after delivery. Nearly 79% of the mothers did not smoke during pregnancy, 8% smoked 1–5 cigarettes a day, and 14% smoked >5 cigarettes a day. Several important covariates were included in the analysis: gender; psychosocial and obstetric adversity; prenatal maternal stress; and lifetime nicotine dependence, alcohol abuse, and cannabis abuse in the offspring. Lifetime ADHD symptoms were measured using structured instruments at 5 points between the ages of 2 and 15 years. Novelty seeking was assessed at age 19 years. For the present study, at age 25 years participants underwent a test of behavioral inhibition while undergoing functional MRI.

Results: As expected, offspring of mothers who smoked had higher rates of smoking and nicotine dependence, higher levels of psychosocial adversity, and more ADHD symptoms. While performing the test of behavioral inhibition, subjects who were exposed prenatally to tobacco smoke showed a diminished response in the anterior cingulate cortex (p=0.003), right and left inferior frontal gyrus (p=0.04 and p=0.009, respectively), and right supramarginal gyrus (p=0.02) compared with unexposed subjects, after controlling for multiple covariates. Except for the right inferior frontal gyrus, effects of maternal smoking on these outcomes were dose-dependent. The results were affected only slightly when ADHD symptoms and novelty seeking were included in the model as additional covariates. For some of the affected brain regions, decreased levels of activity were associated with the levels of novelty seeking and ADHD symptoms. An effect of maternal smoking was observed on the volume of the right inferior frontal gyrus (p=0.002), but not other structures.

Discussion: The association of prenatal tobacco exposure with ADHD is well established, but there have been few studies of specific mechanisms. The anterior cingulate cortex has been implicated in attention processes, response selection, and error monitoring; and the inferior frontal gyrus more specifically in response inhibition. Lower levels of activation in these areas suggest a lack of flexible cooperation between executive functions, possibly due to a lack of attention regulation.

Holz N, Boecker R, Baumeister S, Hohm E, et al: Effect of prenatal exposure to tobacco smoke on inhibitory control: neuroimaging results from a 25-year prospective study. *JAMA Psychiatry* 2014; doi:10.1001/jamapsychiatry.2014.343. From the Medical Faculty Mannheim/Heidelberg University, Germany; and other institutions. Funded by the German Research Foundation. Two study authors declared financial relationships with commercial sources.
**Soft Drink Additive and ADHD Symptoms**

According to results of a survey in college students, high consumption of soft drinks containing sodium benzoate is associated with ADHD symptoms.

**Background:** Sodium benzoate is a commonly used preservative found mainly in fruit-flavored sodas, teas, Italian sodas, and coffee drinks containing syrups. Its effects on behavior have been demonstrated in controlled studies in preschool and elementary school-age children.

**Methods:** A questionnaire was completed by undergraduate students attending large lecture classes at a U.S. university. The survey included general questions about demographic factors; health; physical activity; dietary supplements; physical or mental diagnoses; and drug prescriptions. Also included was a food frequency questionnaire designed to estimate the consumption of sodium benzoate-rich beverages. ADHD symptoms were assessed with a screening version of the Adult ADHD Self-Report Scale.

**Results:** Of the 475 students who completed the surveys, 25 were excluded from the analysis because they had a diagnosis of ADHD, were taking ADHD medication or other psychotropic agents, or took supplements containing serotonin precursors. Of the remaining 450 students, 125 were male. The mean age of participants was 22 years.

Students drank an average of 19 sodium benzoate-containing beverages per month. The 67 students who reported high levels of ADHD symptoms also reported greater sodium benzoate intake than other students: 35 vs. 17 servings per month. Sodium benzoate intake was significantly associated with ADHD symptom scores, both in an unadjusted analysis (p=0.001) and after adjusting for gender, physical activity, and other covariates (p=0.003).

**Discussion:** Sodium benzoate has been found to inhibit dopaminergic transmission in animal models. In the brain, sodium benzoate inhibits the activity of an enzyme that degrades D-serine, an agonist of excitatory glutamate N-methyl D-aspartate (NMDA) receptors and modulator of attention and behavior. The FDA generally recognizes sodium benzoate as safe, but the Food and Agriculture Organization/World Health Organization recommends an acceptable upper limit of 5 mg/kg body weight per day, an amount that may be exceeded by high consumers of sodas and juices. A causal link cannot be inferred in the present study as a result of the cross-sectional design; further investigation is warranted.


From Benedictine University, Lisle, IL; and other institutions. Funded by the Arizona State University Foundation’s Nutrition Research Fund. The authors declared no potential conflicts of interest.

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**Prenatal SSRI Exposure and Autism Risk**

Results of a population-based case-control study suggest that prenatal exposure to SSRIs may be associated with an increased risk of autism spectrum disorder (ASD) in boys. However, underlying maternal depression and its genetics may be a cofactor in the development of ASD, and the benefits and harms of treating maternal depression should be carefully weighed.

**Methods:** Study participants were families enrolled in the California-based Childhood Autism Risks from Genetics and the Environment (CHARGE) Study. The present case-control analysis was based on families with a child aged 2–5 years who had a confirmed ASD diagnosis (n=492) or other developmental delay (n=154). A comparison group of 320 children with typical development, frequency-matched for age, gender, and geographic location, was also included. All children were screened for ASD, and those who screened positive were evaluated.
Results: Children were evaluated at a mean age of about 3.5 years. More than 80% of the ASD and control groups were boys. Two-thirds of the sample was born before the FDA revised SSRI labeling to warn of prenatal risks in 2003. A total of 48 women, 5% of the study population, reported taking SSRIs during pregnancy.

In a multivariate analysis of all of the study children, those exposed to SSRIs did not have elevated risk of ASD or developmental delay. However, when genders were analyzed separately, exposure in boys nearly tripled the associations with ASD (odds ratio,* 2.92) and developmental delays (odds ratio, 3.39). In boys, ASD was associated predominantly with first-trimester exposure and developmental delays were associated with exposure in the second and third trimesters. No significant associations were found in girls, but the sample was too small for reliable analysis.

Discussion: The association of SSRIs with developmental disorders is biologically plausible and supported by other research. SSRIs cross the placenta, reduce serotonin reuptake in the placenta and fetus, and may reduce uterine blood flow, leading to fetal hypoxemia. Given the low rate of exposure in pregnancy, it is unlikely that SSRIs have contributed much to the increase in autism diagnoses over time, the authors say. Too few girls were exposed to SSRIs to analyze their risks separately, but the stronger effects in boys compared with the combined analysis suggests possible effect modification by gender. The association of SSRIs with other developmental delays is based on small numbers and requires further investigation.


*See Reference Guide.
about 1 point in the controls. There were no significant differences among the groups in rates of elevated serum triglycerides, cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or fasting glucose.

**Discussion:** Experience suggests children and adolescents appear to have more pronounced weight gain with atypical antipsychotics than adults. Previous studies of these agents' effects on metabolic parameters suggest a similar spectrum of adverse effects to adults, but these investigations have been inconclusive due to small sample size and varying durations of follow-up. The authors note that the duration of observation in this study may have been too short to detect metabolic effects of antipsychotic-induced weight gain. Alternatively, children may be less vulnerable to these effects than adults because they are more active.


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

**Reference Guide**

**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.

**Noninferiority Trial:** A clinical trial design that shows whether a new treatment is equivalent to standard treatment.

**Number Needed to Treat (NNT):** Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

**Odds Ratio:** A comparison of the probability of an event in 2 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.

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