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Trigeminal Nerve Stimulation for ADHD

In an open-label pilot study, trigeminal nerve stimulation (TNS) was feasible and well tolerated and showed preliminary evidence of efficacy in children with ADHD.

Background: TNS is a noninvasive neuromodulation method currently under investigation for treatment of epilepsy and major depressive disorder. It is safe and well tolerated in adults but has not previously been investigated in pediatric patients. Treatment involves wearing a small stimulating device on the clothing and applying bilateral electrodes to the forehead to stimulate both V_1 branches of the trigeminal nerve.

Methods: The present exploratory study was carried out in unmedicated patients, aged 7–14 years, with ADHD of at least moderate severity and high scores on both the inattentive and hyperactive/impulsive subscales of the ADHD Rating Scale IV (ADHD-RS-IV). All patients underwent 8 weeks of TNS, administered by the parents for 7–9 hours every night. Each child's device was set to provide stimulation that was perceptible but below the threshold of discomfort. Treatment adherence was measured with a parent-completed diary and by weekly interviews. The primary ADHD outcome measure was the ADHD-RS-IV, completed at weeks 4 and 8.

Results: A total of 24 children (mean age, 10 years) started TNS treatment. Two patients dropped out before week 4 and another before week 8, all for unknown reasons, resulting in a final sample size of 21 patients, all of whom completed treatment. Based on treatment diaries, nightly compliance was 100% in these 21 families. There were no reported problems with implementing TNS therapy.

After TNS treatment, patients demonstrated robust improvement in the investigator-rated ADHD-RS-IV and the parent-rated Conners Global Index ($p<0.0001$ for both). Improvements were evident for both the inattentive and hyperactive/impulsive subscales ($p<0.0001$ for each). The majority of patients (64%) were rated as improved or very much improved on the Clinical Global Impression–Improvement scale at week 4; this increased to 71% at week 8.

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Although patients did not meet diagnostic criteria for depression, they did show dimensional-score improvement in depressive symptoms. They also improved in parent-reported executive functioning and some aspects of sleep.

No patient discontinued the study due to adverse events. Potentially treatment-related adverse events were transient headaches (n=2) and eye twitching (n=1), which resolved with no intervention and alternative placement of the electrodes, respectively.

McGough J, Loo S, Sturm A, Cowen J, et al: An eight-week, open-trial, pilot feasibility study of trigeminal nerve stimulation in youth with attention-deficit/hyperactivity disorder. *Brain Stimulation* 2014; doi 10.1016/j.brs.2014.11.013. From the University of California, Los Angeles. **Funded by NeuroSigma, Inc.; and other sources. The authors did not include disclosure of potential conflicts of interest.**

Early Intervention and Young Adult Psychopathology

In a randomized trial of high-risk young people, participation in a multicomponent intervention beginning in kindergarten was associated with lower rates of psychopathology, violent crime, and drug offenses at age 25 years.

Methods: The NIH-funded Fast Track prevention program was carried out at 4 sites in the U.S. beginning in 1991. Participants were "early starters"—i.e., children who showed evidence of antisocial development while in kindergarten. Participating elementary schools in poor, high-crime neighborhoods were randomly assigned to receive the Fast Track intervention or to act as controls. Nearly 10,000 kindergartners were evaluated for behavioral risk based on information from parents and teachers, and approximately 900 with the highest risk scores were enrolled in the trial and received either Fast Track or no intervention, based on the school they attended.

The program was manualized, and a full description can be found at http://fasttrackproject.org. Interventions in elementary school were geared mostly toward improving peer interactions and social competence and included group training of parents, children, and parent-child pairs; tutoring; teacher involvement; and home visits. Additional training in middle and early high school focused on adolescent development, drugs and alcohol, and employment issues. Program participation ended with completion of the 10th grade. Data for the present analysis were obtained when participants were 25 years old and included administrative records and interviews with the participant and a peer of his or her choice. (Study results from earlier time points have been reported in several previous publications.) The analysis of outcomes was adjusted for 22 demographic, socioeconomic, and other variables that were measured prior to the intervention.

Results: Participants in the Fast Track program were less likely than their peers to have evidence of an internalizing, externalizing, or substance use disorder (odds ratio,* 0.59; p=0.001). This result was consistent in separate analyses of all subgroups evaluated: males and females, high- and moderate-risk individuals, those racially identified as African- or European-Americans, and those at all 4 study sites. The number needed to treat* for prevention of 1 case of a psychiatric disorder was 8. Intervention decreased the rate of violent crime convictions by 31% and that of drug convictions by 35%. Fast Track participants were less likely to engage in risky sexual behavior and to spank their own children. The program was associated with higher self-ratings of well-being, but not general health or personal strength. Also unaffected were educational attainment and employment.

Dodge K, Bierman K, Coie J, Greenberg M, et al: Impact of early intervention on psychopathology, crime, and well-being at age 25. *American Journal of Psychiatry* 2015;172 (January):59–70. From Duke University, Durham, NC; and other institutions. **Funded by the NIMH; and other sources. Six study authors declared financial relationships with commercial sources; the remaining authors declared no conflicts of interest.**

***See Reference Guide.**

Antidepressant Monotherapy and Manic Switching

In a group of children and adolescents with bipolar depression, antidepressant monotherapy was associated with an increased risk of manic switching compared with second-generation antipsychotic monotherapy. No difference in risk was found between antidepressant monotherapy and mood stabilizer monotherapy, or between antidepressant polytherapy (i.e., antidepressant with either an antipsychotic or a mood stabilizer) and antipsychotic–mood stabilizer combinations.

Methods: A cohort of patients, aged 6–18 years, receiving treatment for bipolar depression between 2003 and 2007 was assembled using Medicaid claims data from 4 large states. The 4147 patients were divided into 5 mutually exclusive treatment groups based on their medication during the 30 days surrounding the index diagnosis of bipolar depression: antidepressant monotherapy (n=179); antipsychotic monotherapy (n=1047); mood stabilizer monotherapy (n=570); antidepressant polytherapy (n=445); and antipsychotic–mood stabilizer polytherapy (n=1906). Manic switch was identified as treatment-emergent if it occurred within 6 weeks after the initiation of bipolar depression treatment.

Results: During follow-up, rates of manic switch ranged from 8% to 11% across the treatment groups. After controlling for all observable confounders (e.g., demographics, comorbid conditions, physician factors), antidepressant monotherapy was associated with a higher rate of manic switching than antipsychotic monotherapy (hazard ratio,* 2.87). Risk was numerically, but not statistically, higher with antidepressant monotherapy versus mood stabilizer monotherapy and with antidepressant polytherapy versus antipsychotic–mood stabilizer therapy. In all analyses, a history of a prior manic episode was by far the strongest predictor of a manic switch (hazard ratio, 14).

Discussion: Based in part on the belief that childhood-onset bipolar disorder is more severe and volatile than the adult-onset form, pediatric guidelines are more conservative in recommending the use of antidepressants. Adjunctive antidepressant use is common in young patients with bipolar disorder, but antidepressant monotherapy is not, according to prior research. The results of the present study, the first to assess risk of manic switching in children and adolescents, support the belief that a concomitant antipsychotic or mood stabilizer can reduce the risk of antidepressant-induced manic switching.

Study Rating*—12 (86%): This study met most criteria for an observational study, but the source of funding was not stated.

Bhowmik D, Aparasu R, Rajan S, Sherer J, et al: Risk of manic switch associated with antidepressant therapy in pediatric bipolar depression. *Journal of Child and Adolescent Psychopharmacology* 2014;24 (December):551–561. From the College of Pharmacy, University of Houston, TX; and other institutions. **Source of funding not stated. The authors declared no conflicts of interest.**

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Predictors of Suicidal Behavior in ADHD

In adolescents with ADHD, suicidal behavior was linked with several modifiable risk factors in a cross-sectional study. The factors—depression, parent-child conflict, victimization trauma, and social impairment—may be useful in identifying young people at risk for suicide and could be targets for psychosocial or pharmacological interventions.

Methods: Study participants were 101 adolescents, aged 11–18 years, enrolled in a longitudinal study of depression risk factors in ADHD. All participants met DSM-IV-TR diagnostic criteria for ADHD. As part of the larger study, patients underwent a baseline assessment that provided

data for the present analysis. Adolescents and their parents underwent separate interviews with the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (KSADS-PL). Suicidal behavior was defined as suicidal gestures, suicide attempts, or self-injurious behaviors carried out in the presence of suicidal ideation. These behaviors were identified by interviewers after weighing information from both the adolescent and the parent and resolving any conflicts in an individualized manner. Potential correlates of lifetime suicidal behaviors were measured using the KSADS-PL and other standardized rating scales.

Results: The final sample included 37 girls and 64 boys; 31 reported lifetime suicidal ideation. Of these, 28 reported lifetime suicidal behaviors. Adolescents with suicidal behavior were older, were more likely to be female, and had a higher lifetime prevalence of depressive, externalizing, or substance use disorders than the rest of the sample. They also had higher levels of functional impairment, particularly in the areas of peer and family relationships, interest and activities, and parent-child conflict. Suicidal behavior was also associated with trauma based on victimization events; specifically, adolescents who engaged in suicidal behavior were more likely to have experienced domestic violence or physical abuse or to have been kidnapped by a noncustodial parent. They were also more likely to have had a psychiatric hospitalization or to have received antidepressant medication. Contrary to the investigators' expectation, adolescents with suicidal behavior did not have increased ADHD severity.

In a multivariate analysis, several variables remained associated with suicidal behavior after adjusting for age, gender, and lifetime diagnosis of major depressive, externalizing, or substance-use disorders. Depression remained the strongest multivariate risk factor, with an odds ratio,* of 7.0 (p=0.001). The remaining factors were parent-child conflicts (odds ratio, 3.2; p=0.003) and the number of victimization events (odds ratio, 1.4; p=0.03).

Discussion: The association of depression with suicidal behavior in adolescents with ADHD is well known. The present results indicate that potentially modifiable environmental factors and impairment are additional predictors of suicidal behavior. These factors could be targeted with pharmacological or psychosocial treatments to lessen risk of suicide in patients with ADHD.

Daviss W, Diler R: Suicidal behaviors in adolescents with ADHD: associations with depressive and other comorbidity, parent-child conflict, trauma exposure, and impairment. *Journal of Attention Disorders* 2014;18 (November):680–690. From the University of Pittsburgh, PA; and Geisel School of Medicine at Dartmouth, Hanover, NH. **Funded by the National Alliance for Research on Schizophrenia and Depression; and the NIMH. One study author declared financial relationships with commercial sources; the remaining author declared no conflicts of interest.**

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Web-Based Interventions for Depression, Anxiety

According to results of a systematic review, evidence for the effectiveness of web-based or mobile interventions for young people with internalizing problems is limited. However, the limited evidence suggests they may be viewed as a gateway or an adjunct to, rather than a replacement for, face-to-face treatment.

Methods: A comprehensive literature search was undertaken in order to gather information published since 2009 when a previous review was conducted. Included articles were English-language reports, published or unpublished, that became available between 2000 and 2013. The review's focus was internet-based interventions and mobile apps designed to prevent or treat symptoms of anxiety or depression or for suicide prevention in children (aged 5–12 years), adolescents (aged 13–17 years), and/or emerging adults (aged 18–25 years). The review excluded case series and studies of virtual-reality exposure treatments or messaging-only apps. Study outcomes were estimated using effect size.* See table (next page) for intervention details.

Web-Based Interventions for Depression/Anxiety in Youth			
Program	**Description**	**Structure**	**Clinician Involvement**
CATCH-IT	Based on CBT and interpersonal therapy; designed to prevent or reduce depressive symptoms	14 sequential modules Includes skill-building exercises, feedback, and internet-based rewards	Self-guided; enhanced versions can include motivational interviewing or brief advice
Master Your Mood (MYM)	Based on CBT for youth with depressive symptoms	6 weekly sessions (90 min each) with a chat room-based presentation Includes psychoeducation, self-monitoring, cognitive restructuring, participation in pleasant activities, and relapse prevention	Therapist-assisted
MoodHelper	CBT-based intervention for young adults with depression	4-modules: graphically-displayed depression scale; journal; interactive tutorials; cognitive restructuring tool	Self-guided
Feeling Better	CBT-based internet intervention designed to reduce depression, anxiety, and stress in college students with mild-to-moderate symptoms	11 modules: 4 core skills delivered in 7 sequential modules plus 4 optional modules Core skills: psychoeducation; goal-setting; cognitive restructuring; stress management Optional: sleep hygiene; anger management; review of nonpsychological treatments, premenstrual syndrome, and mood	Minimal therapist assistance
Mobiletype	The only identified mobile app; designed to help clinicians identify and manage depression, anxiety, and stress	Self-monitoring of activities, mood, stress, alcohol and cannabis use, sleep, exercise, and diet Random prompts to complete self-monitoring entries	Physician-review upon completion
MoodGYM	CBT-based intervention adapted from an adult program for use by adolescents to treat or prevent depression	5 sessions (30–60 min each) that include animated demos, quizzes, and homework covering relaxation, problem solving, cognitive restructuring, assertiveness, self-esteem, and relationships	Self-guided
Problem-Solving Therapy (PST)	CBT-based internet program aimed at preventing adolescent depression and anxiety	5 weekly sessions focused on problem solving, strategies to eliminate negative thoughts and enhance positive thoughts, and goal setting	Minimal therapist assistance
BRAVE ONLINE	CBT-based, internet intervention for youth with established separation anxiety disorder, generalized anxiety disorder, social or specific phobia	10 weekly sessions (60 min each) using real-life examples, games, quizzes, and homework to cover psychoeducation, relaxation strategies, cognitive restructuring, graded exposure, and problem solving 2 booster sessions after completion 5 parent sessions focused on psychoeducation, contingency management, relaxation training, and anxiety management strategies	Minimal therapist assistance
Cognitive Bias Modification	Internet-delivered, attention bias modification program for youth with symptoms of social phobia and test anxiety	20 sessions (40 min twice weekly) focused on imagination training, ambiguous social situations, and visual probes	Self-guided

Results: The authors identified 25 articles describing 9 programs: 8 web-based and 1 mobile app. A total of 14 studies were randomized controlled trials, and the rest were open studies, follow-up studies, and secondary-data analyses. Sample sizes ranged from 14 to >8000. Of the 9 programs, 3 were for depression, 2 for anxiety, and 4 for either problem; no programs for suicide prevention were identified. All programs were based on cognitive behavioral therapy (CBT).

The BRAVE ONLINE program was the only intervention with sufficient evidence to classify it as probably efficacious. MoodGym and MYM were judged possibly efficacious; CATCH-IT, Feeling Better, and MoodHelper were deemed experimental; and PST, Mobiletype, and CBM were considered of questionable efficacy. BRAVE ONLINE is the only program developed for patients with a full diagnosis, rather than a high-risk group or one with subthreshold symptoms. It has been the subject of 3 randomized controlled trials, which reported moderate-to-large effect sizes. However, a major limitation of the evidence is that all of the studies were conducted by the programs' developers.

Reyes-Portillo J, Mufson L, Greenhill L, Gould M, et al: Web-based interventions for youth internalizing problems: a systematic review. *Journal of the American Academy of Child and Adolescent Psychiatry* 2014;53 (December):1254–1270. From the New York State Psychiatric Institute, Columbia University Medical Center, New York, NY. **Funded by the Sallie Foundation Child and Adolescent Mental Health Technology Program. Six study authors declared financial relationships with commercial sources; the remaining author declared no conflicts of interest.**

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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 Treat: 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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Mindfulness Therapy in Familial Bipolar Risk

In a small pilot study, group mindfulness-based cognitive therapy for children (MBCT-C) reduced anxiety in young people with anxiety disorders who were also at familial risk for bipolar disorder. The treatment has the potential to reduce medication exposure and possibly prevent the onset of bipolar disorder.

Background: Parental bipolar disorder is associated with increased risk of mood and anxiety disorders in children and adolescents. Presence of an anxiety disorder further increases the risk of bipolar disorder in these patients. Antidepressants are often used to treat these symptoms, but may be poorly tolerated or induce mania in this population. Nonpharmacological treatments that encourage children and parents to be more proactive in symptom prevention and management and that teach skills for managing emotions are needed.

Methods: Participants were recruited from an ongoing cohort of children and adolescents at risk for bipolar disorder. Each had at least 1 parent with bipolar I disorder, met diagnostic criteria for an anxiety disorder (generalized anxiety disorder, separation anxiety disorder, panic disorder, and/or social phobia/social anxiety disorder), and met symptom thresholds on the Hamilton Anxiety Rating Scale (HAM-A) and the Pediatric Anxiety Rating Scale (PARS). All patients received manualized MBCT-C, which consisted of 12 weekly, 75-minute sessions administered in separate age groups: 9–12 years and 13–16 years. Treatment emphasized mindfulness practices (e.g., body scan, meditations, breath work), awareness, and conscious regulation of emotions. Unlike conventional CBT, there was little emphasis on changing thought content. The primary study outcome measures were the clinician-rated PARS and the patient-reported State-Trait Anxiety Inventory (STAI).

Results: The 10 patients, 5 in each age group, completed 89% of the scheduled treatment sessions. Patients experienced significant reductions from baseline in clinician-rated anxiety symptoms—with PARS scores decreasing from 11 to 4 ($p<0.01$), and in self-reported trait anxiety—with a decrease in STAI score from 42 to 34 ($p=0.03$). Self-reported STAI state anxiety

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was not significantly improved. In addition, patients in the older age group had significantly greater increases in mindfulness and reductions in emotional lability than the younger children. Nine of the participants had remission of clinician-rated anxiety, defined as a final PARS score <8.

In questionnaires administered after treatment, 9 children reported that the program was helpful or very helpful and they would recommend it to a friend, that treatment helped them at school and home, and that they would continue using the mindfulness techniques. Eight said they felt less worried, more patient, and better able to manage anger. Three participants reported that the mindful breathing exercises were the most useful part of the program. Parent responses were more equivocal: Of 6 who completed the survey, 4 indicated their child was less anxious and 5 agreed that the program was helpful, but 4 were neutral or unsure about the effect of treatment on the child's anger management and 5 were neutral or unsure about increased positive interactions with others.

Discussion: Although they need to be replicated in larger studies, the results of this pilot study suggest that MBCT-C decreases anxiety and improves emotion regulation in children at risk for bipolar disorder. The intervention appears to be acceptable and could potentially prevent the onset of bipolar disorder in these patients.

Cotton S, Luberto C, Sears R, Strawn J, et al: Mindfulness-based cognitive therapy for youth with anxiety disorders: a pilot trial. *Early Intervention in Psychiatry* 2015; doi 10.1111/eip.12216. From the University of Cincinnati College of Medicine, OH; and other institutions. **Funded by the University of Cincinnati; the NIH; and other sources. The authors did not include disclosure of potential conflicts of interest.**

Psychosocial Treatments for Eating Disorders

According to an updated review, the landscape of evidence-based psychosocial treatments for eating disorders has changed little since the last major review in 2008. The update included clinical trials of psychosocial treatments for eating disorders in adolescents (aged 13–18 years) and children (aged 6–12 years), published in English between 1985 and 2011. The investigators also identified 7 completed, but not-yet-published, clinical trials. The review was based on 98 articles. The evidence for treatments was categorized according to a numeric scale, from level 1 (well established) to level 5 (questionable efficacy).

Anorexia Nervosa: A total of 12 randomized controlled trials, including 6 completed since 2008, describe treatment of anorexia nervosa in 1060 adolescents. Family therapy with a behavioral focus (FT-B; also called family-based treatment or Maudsley Family Therapy) continues to be the only well-established treatment (level 1) for adolescent anorexia. Family therapy focused on the family system (FT-S) and insight-oriented individual psychotherapy were judged to be probably efficacious (level 2). Some evidence supports broadly-focused (or enhanced) cognitive behavioral therapy (CBT) and cognitive training, but these interventions are considered experimental (level 4).

Bulimia Nervosa: There are only 2 published clinical trials examining psychosocial treatments for adolescents with bulimia. Evidence suggests that CBT-guided self-help and FT-B are both possibly efficacious (level 3). Other studies suggest CBT and supportive psychotherapy are experimental (level 4) in bulimia.

Binge Eating Disorder: Preliminary studies in adolescents with binge eating disorder provide an experimental rating (level 4) for dialectical behavioral therapy and interpersonal therapy.

Avoidant Restrictive Food Intake Disorder (ARFID): A new entity in DSM-5, ARFID is a disorder of restricted food intake without shape or weight concerns, associated with disturbances in development and functioning. There are no empirical studies of psychosocial treatments for this disorder.

Discussion: Recovery rates for adolescents with eating disorders range from 30% to 40% with existing treatments. Several emerging treatments appear to warrant further study. Adjunctive cognitive training that targets cognitive inflexibility and over-focusing on details may be useful in increasing motivation and altering cognitive style, but it does not appear to affect eating disorder-related behaviors. Dialectical behavior therapy, which targets emotion regulation, appears to be effective in adults but has only minimal evidence in adolescents.

Lock J: An update on evidence-based psychosocial treatments for eating disorders in children and adolescents. *Journal of Clinical Child & Adolescent Psychology* 2015; doi 10.1080/15374416.2014.971458. From Stanford University School of Medicine, CA. **Source of funding not stated. The author did not include disclosure of potential conflicts of interest.**

QT Changes with Antipsychotics

Antipsychotic drugs confer little risk of corrected QT (QTc) prolongation in otherwise healthy children and adolescents, according to results of a meta-analysis.[1] However, clinicians should remain vigilant for underlying medical conditions or other risk factors for electrocardiogram (ECG) abnormalities when prescribing antipsychotics.[2]

Methods: A literature search identified all prospective trials (randomized or not and with or without a placebo or other comparison group) of first- or second-generation antipsychotic drug therapy, prescribed for treatment of a psychiatric condition in patients aged <18 years (n=55 studies). The studies evaluated nearly 5500 patients treated with 9 different antipsychotics or placebo. Four studies evaluated ECG changes as their primary outcome, and the rest included these data as a secondary safety endpoint.

Results: Ziprasidone (10 studies, with 13 treatment arms, in >500 patients) was associated with significant QTc prolongation (8.74 milliseconds [ms]; p<0.001). Risperidone was associated with modest prolongation compared with baseline (1.68 ms; p=0.001), but not compared with placebo. Aripiprazole was associated with a small decrease in the QTc interval (1.44 ms; p=0.017). None of the other second-generation antipsychotics was associated with QTc change, although for some drugs the sample sizes were small and studies showed significant heterogeneity. The meta-analysis did not include single studies of 2 older antipsychotics, with small sample sizes. These showed average QTc prolongation from baseline with pimozide (25 ms) and haloperidol (8 ms).

Thresholds for clinically significant QTc prolongation varied among studies. Using the studies' individual cut-offs, about 2% of patients experienced QTc prolongation overall, including 3% of those treated with ziprasidone and 2% of those receiving placebo. Only 1 of the 500 patients exposed to ziprasidone, and none exposed to the other antipsychotics, had a >500 ms increase. Increases from baseline of >60 ms, another clinical threshold, occurred in about 1% of all study participants: 2.5% of those taking ziprasidone, about 1% of those exposed to risperidone, 1% of the pooled placebo groups, and no other patients.

Discussion: The relationship between QTc prolongation and cardiovascular events is controversial; however, it is the best available clinical marker for risk of Torsades de pointes. QTc prolongation is a known adverse effect of antipsychotics. The results of the present study regarding ziprasidone and aripiprazole mirror observations in adults. Pimozide, also associated with QTc prolongation in adults, should be avoided in young patients with relevant risk factors for cardiac conduction abnormalities. Other risk factors that should be taken into consideration when prescribing antipsychotics include family history of long QT syndrome or sudden death, prior QTc prolongation >450 ms, palpitations at rest, and dizziness or syncope on exertion.

Editorial. Routine ECG screening is not indicated for healthy young patients. However, small QTc changes, which are not clinically relevant for healthy patients, may become problematic as a consequence of longer-term treatment, polypharmacy, medical comorbidity, or drug misuse.

Study Rating*—18 (100%): This study met all criteria for a systematic review and meta-analysis.

[1]Jensen K, Juul K, Fink-Jensen A, Correll C, et al: Corrected QT changes during antipsychotic treatment of children and adolescents: a systematic review and meta-analysis of clinical trials. *Journal of the American Academy of Child and Adolescent Psychiatry* 2015;54 (January):25–36. From Mental Health Services Capital Region and the University of Copenhagen, Denmark; and other institutions. **Funded by the Dr. Sofus Carl Emil Friis and Hustru Olga Friis Scholarship; and other sources. Two study authors disclosed financial relationships with commercial sources; the remaining 3 authors declared no conflicts of interest.**

[2]Munshi K, Alexander M, Hammerness P: Corrected QT interval changes with atypical antipsychotics [editorial]. *Journal of the American Academy of Child and Adolescent Psychiatry* 2015;54 (January):9–10. From Boston Children's Hospital, MA. **Two authors disclosed financial relationships with commercial sources; the remaining author declared no conflicts of interest.**

Drug Trade Names*: aripiprazole—*Abilify*; haloperidol—*Haldol*; pimozide—*Orap*; risperidone—*Risperdal*; ziprasidone—*Geodon

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Behavioral Intervention for ADHD Sleep Problems

In a randomized trial, a brief sleep intervention produced multiple benefits in children with ADHD and sleep problems and in their families. ADHD symptom severity, the primary study outcome, was modestly improved.

Methods: The study enrolled children, aged 5–12 years, who had ADHD and parent-reported moderate-to-severe sleep problems. Patients were required to meet American Academy of Sleep Medicine diagnostic criteria for ≥1 sleep disorder or for anxiety leading to insomnia. Families were randomly assigned to receive either the sleep intervention or usual clinical care. Parents in the intervention group were offered 2 face-to-face consultations about sleep with a clinician (either a psychologist or a trainee pediatrician). The first session included an assessment, goal-setting, and a management plan tailored to the child's sleep problem. The plan was reinforced in the second session 2 weeks later, and then again with a follow-up telephone call. The primary study outcome was ADHD symptoms, which were assessed using the ADHD Rating Scale-IV, parent and teacher versions, at 3 and 6 months post-intervention.

Results: A total of 114 families received the intervention, and 122 participated in the control group. Three-fourths of the children were taking stimulants, and 9–15% were taking other medications. Most children had a comorbid externalizing or internalizing disorder.

Follow-up questionnaires were completed by 164 families (79 in the intervention group) at 3 months and 196 families (99 intervention) at 6 months. At 3 months, the intervention was associated with a statistically significant but modest improvement in parent-reported ADHD symptoms, relative to controls ($p=0.03$; effect size,* 0.3), with the greatest improvement for inattentive symptoms. These effects were maintained and slightly strengthened at 6 months (effect size, 0.4). Teacher-reported ADHD symptom scores did not differ between the 2 groups at either 3 or 6 months.

Nearly all secondary study outcomes showed greater improvement with the intervention than in the control group. Those who received the intervention had a lower prevalence of sleep problems at 3 months (56% vs. 30%; odds ratio,* 0.30; $p<0.001$), with a number needed to treat* of 4. Results were similar, although somewhat attenuated, at 6 months. Children who had the intervention had a greater reduction in behavioral difficulties and larger

improvements in psychosocial quality of life, daily functioning, and teacher-reported behavior difficulties, with effect sizes in the small-to-medium range. At 3 months, parents reported fewer missed work days or days late to work, although this effect was not sustained at 6 months.

Discussion: Sleep problems are common in children with ADHD for several reasons, including shared neurobiological pathways, effects of stimulant medication, comorbid problems such as anxiety, and poor sleep practices. The intervention in the present study was designed to be widely applicable in primary- or secondary-care clinical practice. Its effects on ADHD symptoms were similar to more extensive, ADHD-targeted behavioral interventions and wider-ranging than those shown with melatonin.

Hiscock H, Sciberras E, Mensah F, Gerner B, et al: Impact of a behavioural sleep intervention on symptoms and sleep in children with attention deficit hyperactivity disorder, and parental mental health: randomised controlled trial. *British Medical Journal* 2015; doi 10.1136/bmj.h68. From Royal Children's Hospital, Parkville, Australia; and other institutions.
Funded by the Australian National Health and Medical Research Council. The study authors declared no conflicts of interest.

***See Reference Guide.**

Irritability in ADHD

According to an analysis of data from the Multimodal Treatment Study of Children with ADHD (MTA), irritability is a separate dimension within the spectrum of oppositional defiant disorder symptoms. Stimulants alone are helpful in reducing irritability in children with ADHD and are even more effective when combined with behavioral therapy, according to the analysis.

Methods: Investigators conducted secondary analyses of data from the multicenter U.S. MTA trial, which compared 4 treatments: medication management, behavior therapy, both, or control treatment consisting of the parents' choice of therapy in the community. The active treatments were delivered for 14 months according to specified protocols. The analysis was based on the entire study cohort of 579 children, aged 7–10 years at study entry. ADHD symptoms were assessed using the 18-item, parent-rated Swanson, Nolan, and Pelham (SNAP) rating scale. Irritability and headstrong behavior were assessed using the relevant items from the SNAP oppositional defiant disorder subscale: 3 for irritability ("Loses temper," "Is touchy or easily annoyed by others," and "Is angry and resentful"), and 4 for headstrong behavior ("Argues with adults," "Actively defies or refuses adult requests or rules," "Does things deliberately that annoy other people," and "Blames others for his or her mistakes or misbehavior").

Results: Both the irritability and headstrong behavior items showed high internal consistency. Irritability at baseline was predictive of irritability at the 14-month follow-up, and headstrong behavior predicted further headstrong behavior; but the 2 types of behavior were not predictive of each other. Irritability was a strong predictor of internalizing problems, while headstrong behavior was more predictive of externalizing problems. Irritability and headstrong behaviors each contributed independently to impairment.

In the MTA population, all ADHD treatments were effective in reducing irritability. Effects were largest for combined medication and behavioral treatment (effect size,* 0.82), followed by medication management (effect size, 0.63), community comparison (effect size, 0.48), and behavior therapy alone (effect size, 0.42). Irritability did not have a differential effect on the reduction in ADHD symptoms with treatment.

Discussion: Previous research suggests oppositionality is made up of 2 or 3 constructs, the third being hurtful behavior, which could not be measured using the SNAP. The results of

this study suggest irritability in ADHD contributes to impairment, is more associated with emotional than conduct problems, and shows longitudinal continuity. It has the same structure and correlates as in children without ADHD. Clinicians can be confident that irritability symptoms do not have a negative effect on ADHD treatment outcomes and that treating ADHD improves irritability.

Fernandez de la Cruz L, Simonoff E, McGough J, Halperin J, et al: Treatment of children with attention-deficit/hyperactivity disorder (ADHD) and irritability: results from the Multimodal Treatment Study of Children With ADHD (MTA). *Journal of the American Academy of Child and Adolescent Psychiatry* 2015;54 (January):62–70. From Kings College London, U.K.; and other institutions. **Funded by the National Institute for Health Research. Three study authors disclosed financial relationships with commercial sources; the remaining 3 authors declared no conflicts of interest.**

***See Reference Guide.**

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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.

Number Needed to Treat: 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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CHILD & ADOLESCENT PSYCHIATRY ALERTS

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Bibliotherapy for Nighttime Fears

In a preliminary study, home-based bibliotherapy reduced nighttime fears and avoidant behaviors in young children.[1] The treatment, which involves reading to the child at bedtime and conducting simple exposure exercises, may come to be considered a first-line approach for mild-to-moderate nighttime fears.

Background: The treatment is based on a book called *Uncle Lightfoot, Flip That Switch: Overcoming Fear of the Dark*.[2] The book, designed to be read to the child by an adult at bedtime, tells the story of a young boy who overcomes his fear of the dark by playing exposure games with a supportive character (Uncle Lightfoot). The volume includes a parent guidebook and encourages exercises such as looking for a toy in the dark and identifying sounds.

Methods: Study participants were 9 children, aged 5–7 years, with a primary or secondary diagnosis of specific phobia. Children and their mothers visited the study clinic for initial evaluation. Following a randomly selected 1, 2, or 3 week baseline, they returned to receive the book and instructions. Response was evaluated at completion (4 weeks) and again 1 month post treatment. Mothers were instructed to read chapters from the book to the child each evening and to play as many of the exposure games as the child was willing. The primary study outcome was change from baseline in the Anxiety Disorders Interview Schedule for Children, Parent Version (ADIS-P).

Results: All families completed the treatment, and 6 of the parents read through the book at least twice, as recommended. Mothers read to the child an average of nearly 6 nights during the first week and about 4 nights per week afterward. Children showed significant change in ADIS-P symptoms from baseline to 4 weeks ($p=0.011$) and to 1-month post treatment ($p=0.011$), with improvement remaining stable during the follow-up month. Estimates of reliable change showed that 8 of the 9 children exceeded clinical cutoffs for reliable change in specific phobia, and 3 reached the non-clinical range post treatment.

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Children also showed reduction in avoidant behaviors, which was operationally defined as inability to sleep in their own bed. They slept alone a mean of 2 nights per week before treatment and 5 nights afterward. The children also showed significant improvement on several standardized measures of fear of the dark, nighttime fears, separation anxiety, and fear-related behavior. One parent reported only slight improvement in their child's fear of the dark, 5 indicated moderate improvement, 2 reported major improvement, and 1 said the child was entirely free of their fear. Parents reported a high level of satisfaction with the treatment (mean score, 4.2 on a 5-point scale).

Discussion: Nighttime fears are extremely common in children and are not a separate diagnostic entity, but some children are affected seriously enough to qualify for a diagnosis of specific phobia. Cognitive behavioral therapy (CBT) is the accepted first-line treatment for childhood fear and anxiety. The present study provides initial support for bibliotherapy, an approach that may have superior efficacy to CBT for other anxiety disorders and in somewhat older children.

[1]Lewis K, Amatya K, Coffman M, Ollendick T: Treating nighttime fears in young children with bibliotherapy: evaluating anxiety symptoms and monitoring behavior change. *Journal of Anxiety Disorders* 2015;30 (March):103–112. From the University of Illinois at Chicago; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

[2]Coffman M: *Uncle Lightfoot: Flip That Switch: Overcoming Fear of the Dark*. St Petersburg, FL: Footpath Press; 2012.

Family-Based Therapy for Preadolescent Depression

In a randomized trial, family-based interpersonal psychotherapy (FB-IPT) was effective in the treatment of depression in preadolescents.

Background: There have been few controlled studies of effective treatments for preadolescent depression. Cognitive behavioral therapy is promising, but there is a need for treatment that involves the parents and that addresses interpersonal impairment. FB-IPT is an adaptation of interpersonal psychotherapy that actively involves parents in weekly sessions and directly addresses parent–child conflicts and interpersonal impairment.

Methods: FB-IPT was compared with child-centered therapy (CCT) in 38 patients, aged 7–12 years, who sought treatment at a specialty clinic for youth depression. Patients were allowed to use medication during the trial; 2 met criteria for depression at enrollment despite continuing stable SSRI therapy and another 6 began SSRIs during the initial weeks of psychotherapy, with the investigators' consent. Patients were randomly assigned in a 2:1 ratio to FB-IPT or CCT, the latter an effective supportive treatment that closely approximates usual depression treatment in community mental health. Both treatments were provided in 14 weekly sessions. For FB-IPT, the patient and 1 or both parents were seen either jointly or sequentially, depending on the phase of the intervention. Parents of children receiving CCT could attend the first 10 minutes of their child's session but were not otherwise involved. The primary outcome measure was the Children's Depression Rating Scale, Revised (CDRS-R), with a score <28 indicating remission.

Results: Children who received FB-IPT were more likely than those who received CCT to achieve remission post-treatment (66% vs. 31%; p=0.04). The FB-IPT group had lower CDRS-R scores (27 vs. 35; p=0.002) and superior outcomes on the child and parent versions of the Mood and Feelings Questionnaire.

A path analysis was conducted to determine whether the change in depression was the result of changes in various intermediate treatment outcomes. There were no indirect effects of changes in parent–child conflict on depression, and the mediating effect of reduced anxiety, while greater in FB-IPT, was not statistically significant. FB-IPT-related changes in social

impairment were larger than with CCT (p=0.001) and were linked with improvement in depression, thus partially accounting for the association of FB-IPT with relief of depressive symptoms.

Discussion: The results of this study support the advantage of FB-IPT over supportive therapy; its effects on mediating risk factors of anxiety and social impairment suggest that FB-IPT may act by addressing these mechanisms.

Study Rating:*—15 (88%): This study met most criteria for a randomized controlled trial; however, only 60% of post-treatment assessments were conducted by blinded raters.

Dietz L, Weinberg R, Brent D, Mufson L: Family-based interpersonal psychotherapy for depressed preadolescents: examining efficacy and potential treatment mechanisms. *Journal of the American Academy of Child and Adolescent Psychiatry* 2015;54 (March):191–199. From the University of Pittsburgh School of Medicine, PA; and the Columbia University College of Physicians and Surgeons/New York State Psychiatric Institute. **Funded by the NIMH. Three authors disclosed potentially relevant financial relationships; the fourth author declared no conflicts of interest.**

***See Reference Guide.**

Safety Signals with Antipsychotics

Analysis of data from the FDA Adverse Event Reporting System (FAERS) suggests that antipsychotics are among the top 5 suspect therapeutic drug classes in young patients. Because antipsychotics are being prescribed with increasing regularity for children and adolescents, a data mining study was undertaken to assess the association between these drugs and serious, potentially fatal adverse events.

Methods: More than 4.5 million FAERS reports spanning late 1997 through mid-2011 were screened to identify cases of neuroleptic malignant syndrome (NMS), QT prolongation, leukopenia, and suicide attempts in children aged <12 years who were treated with haloperidol or a second-generation antipsychotic. Four different data mining algorithms, in use by various national regulatory bodies and the World Health Organization, were used to identify signals—events reported at a higher frequency of association than expected. An adverse event was considered drug related when ≥1 of the algorithms detected a signal.

Results: The number of reported cases of each adverse event was small (<15 each); nevertheless, many safety signals were detected. (See table.) Signals for NMS were identified for all drugs except clozapine and ziprasidone, but were larger for haloperidol and aripiprazole than for the other drugs. For QT prolongation, signals were detected only for risperidone and, more strongly, ziprasidone. Leukopenia was associated with quetiapine, risperidone, and especially clozapine. Suicide attempts were associated with haloperidol, olanzapine, quetiapine, risperidone, and aripiprazole.

Safety Signals with Antipsychotics in Children

	NMS	QT Prolongation	Leukopenia	Suicide Attempt
Haloperidol	X			X
Olanzapine	X			X
Quetiapine	X		X	X
Clozapine			X	
Ziprasidone		X		
Risperidone	X	X	X	X
Aripiprazole	X			X

X indicates a statistically significant safety signal

Discussion: Recent studies suggest antipsychotics are not homogeneous with regard to efficacy or safety. The present analysis extends this conclusion to rare, potentially fatal adverse events. Research should be continued in order to obtain a large quantity and variety of data.

Kimura G, Kadoyama K, Brown J, Nakamura T, et al: Antipsychotics-associated serious adverse events in children: an analysis of the FAERS database. *International Journal of Medical Sciences* 2015;12:135–140. From Kyoto University, Japan; and other institutions. **Funded by the Funding Program for Next Generation World-Leading Researchers; and the Japan Society for the Promotion of Science. The authors declared no conflicts of interest.**

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

Mazindol for ADHD: Pilot Study

Treatment with the catecholaminergic agonist mazindol reduced ADHD symptoms in an open-label pilot study in children who had experienced poor response with stimulants.

Background: Mazindol works by blocking norepinephrine and dopamine reuptake, as do stimulants, but has a lower potential for abuse. It is available in Canada and Europe for the short-term treatment of obesity. Mazindol is available in the U.S. as an orphan drug for the treatment of Duchenne muscular dystrophy. It has been studied in sleep disorders such as narcolepsy.

Methods: Study participants were 21 children, aged 9–12 years, with impairing symptoms of ADHD that required a change from their current medication. All had been poor responders to methylphenidate for ≥6 months. After a 10-day washout of all ADHD medications, the children received 1 mg/day mazindol for 7 days. Pharmacokinetic studies were performed starting after the first dose. The primary outcome measure was change from baseline in mean ADHD Rating Scale-IV (ADHD-RS-IV) total score.

Results: ADHD-RS-IV total scores decreased from a mean of 43 before treatment to 18.9 on the last day ($p<0.0001$). Scores returned to baseline levels a week after mazindol discontinuation. A similar pattern was observed for the Conners Parent Rating Scale–Revised: Long ($p<0.0001$). The mean Clinical Global Impression–Severity score decreased from 5.6 to 3.1. Only 2 children had an illness severity score of ≥5 (markedly ill) while on treatment, and 12 had a score of ≤3 (mildly ill). Twelve patients had a CGI–Improvement rating of much or very much improved.

A total of 19 patients experienced adverse events, but none was severe enough to discontinue treatment. One-third had decreased appetite, which was severe but transient in 4 patients. There were no reports of insomnia or changes in blood pressure, heart rate, or ECG parameters.

Konofal E, Zhao W, Laouenan C, Lecendreux M, et al: Pilot phase II study of mazindol in children with attention deficit/hyperactivity disorder. *Drug Design, Development and Therapy* 2014;8:2321–2332. From the Hopital Robert Debre, Paris, France; and other institutions. **Funded by Assistance Publique – Hopitaux de Paris; and Genopharm. One study author disclosed relationships with commercial sources; the remaining 7 authors declared no conflicts of interest.**

Drug Trade Names*: mazindol—*Sanorax*; methylphenidate—*Ritalin

PANDAS/PANS

In the late 1990s, researchers at the NIH described a syndrome of acute-onset tics and/or OCD symptoms associated with a streptococcal infection. Controversy about the validity of this syndrome—termed Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)—continues to exist in spite of supporting biological models and effective treatment studies. More recently it was found that children without a documented streptococcal infection experienced a similar array of acute-onset neuropsychiatric symptoms, and the PANDAS concept was expanded to include nonstreptococcal infection and re-termed Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS). The *Journal of Child and Adolescent Psychopharmacology* recently published a theme issue on PANDAS/PANS, which includes information on the clinical presentation and recommendations for clinical evaluation of suspected PANDAS/PANS. In addition, the issue includes open and controlled treatment results, which are summarized in the following stories in this issue of *Child & Adolescent Psychiatry Alerts*.

Chang K, Koplewicz H, Steingard R: Special issue on pediatric acute-onset neuropsychiatric syndrome. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (1):1–2. From Stanford University School of Medicine, CA; and the Child Mind Institute, New York, NY. **The authors did not include disclosure of potential conflicts of interest.**

Cefdinir for Tics/OCD

Results of a preliminary, randomized, controlled trial suggest that the cephalosporin antibiotic cefdinir may reduce symptoms of OCD and tics in young patients with recent-onset symptoms.

Methods: Study subjects were 20 children, aged 4–13 years (mean age, 7.5 years; 75% male), with new onset tics or OCD symptoms with (n=14) or without (n=6) evidence of an infectious trigger within the previous 6 months. Participants were randomized to receive double-blind treatment with either 14 mg/kg/day cefdinir or placebo for 30 days. OCD symptoms were evaluated using the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and then analyzed by symptom group (i.e., OCD or tics). Phonic and motor tics were measured with the Yale Global Tic Severity Scale (YGTSS).

Results: In the group of children who presented with OCD symptoms, mean CY-BOCS scores decreased from 22.7 at baseline to 14.8 at 30 days in the cefdinir group and from of 18.6 to 13.9 in the placebo group. Although the difference between the groups was not statistically significant, within-group effect sizes* were 1.22 for active treatment, compared with 0.51 for placebo. In the children who presented with tics, YGTSS scores decreased from a mean of 20.4 to 10.9 in the cefdinir group and from 13.5 to 13.4 in the placebo group. Within-group effect sizes were 0.97 and 0.01 in the groups, respectively, but again the between-group difference was not significant.

Four patients (2 in each treatment group) experienced a >50% decrease in OCD symptoms, and 2 patients receiving cefdinir experienced dramatic improvements in tic severity (YGTSS decrease of 20 points). All of the patients with large symptom reductions entered the study with both OCD symptoms and tics.

Discussion: Although the etiology of OCD and tics remains unclear, infectious or immune-based etiology has been implicated for some patients. While preliminary and not statistically significant, the results of this study suggest that antibiotic treatment may be effective for these patients. The large within-group treatment effects appear to warrant further study in fully-powered samples.

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

Murphy T, Parker-Athill C, Lewin A, Storch E, et al: Cefdinir for recent-onset pediatric neuropsychiatric disorders: a pilot randomized trial. *Journal of Child and Adolescent Psychopharmacology* 2015; 25 (1):57–64. From The University of South Florida, Tampa. **Funded by the National Alliance for Research on Schizophrenia and Affective Disorders (NARSAD). Four study authors disclosed relationships with commercial sources; the remaining 2 authors declared no conflicts of interest.**

See Reference Guide.

IV Immunoglobulin for PANDAS

Children with PANDAS have been shown to improve with intravenous immunoglobulin (IVIG) therapy, but long-term outcomes have not previously been reported. To address the issue of long-term efficacy, case files from a clinical practice specializing in the treatment of PANDAS were reviewed.

A total of 12 youths with a confirmed PANDAS diagnosis received IVIG and had sufficient follow-up data for inclusion in the case series. The patients, aged 7–16 years, all underwent IVIG after other treatments—e.g., antibiotics, antidepressants, cognitive behavioral therapy, and steroid bursts—failed to control their neuropsychiatric symptoms. IVIG therapy was completed in a single day. Most patients (9 of 12; 75%) experienced rapid and dramatic resolution of their symptoms after IVIG. One patient experienced remission of symptoms at a slower pace (approximately 12 months), and 2 patients required a second IVIG infusion to achieve complete recovery. As PANDAS is an episodic disorder, recurrence of symptoms is expected. Five patients required a second course of IVIG therapy for recurrence of tics/OCD during follow-up. Long-term follow-up data were available for 11 of the 12 patients, all of whom were reportedly in remission or symptom free at last contact after a range of 12 months to 7 years.

In these 12 patients, IVIG was used as part of a multimodal treatment plan that included ongoing antibiotic prophylaxis and/or other therapies. However, all patients had undergone unsuccessful treatment with other therapies before IVIG, suggesting that the immunomodulatry treatment produced the beneficial effects.

Kovacevic M, Grant P, Swedo S: Use of intravenous immunoglobulin in the treatment of twelve youths with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (1):65–69. From Loyola University School of Medicine, Maywood, IL; and the NIMH, Bethesda, MD. **The authors declared no conflicts of interest.**

Plasma Apheresis for PANDAS

The neuropsychiatric symptoms characteristic of PANDAS have been hypothesized to stem from post-infection autoimmunity, mediated through cross-reactive antibodies. Theoretically, removing the offending autoantibodies should produce symptomatic improvements.

Methods: Between 2009 and 2013, 40 young patients received therapeutic plasma apheresis (TPA) for severe PANDAS at a single university hospital. Follow-up information was available for 35 patients (mean age at TPA, 11.5 years; 23 boys). All patients had received antibiotic therapy without symptom relief, and most had not experienced response with previous steroids (n=5) or IVIG (n=17). Antibiotic prophylaxis was continued throughout the TPA protocol, which involved insertion of a central line and administration of three 1.5 volume therapeutic exchanges over 3–5 days. Long-term follow-up ranged from 6 months to >5 years.

Results: At baseline, 34 of the 35 children were experiencing OCD symptoms. In the 6 months following TPA, 8 patients continued to experience OCD. Tics were present in 22 patients at baseline, but at 6 months only 6 patients continued to experience them. At the 6-month evaluation, parents reported their children's symptoms had decreased by an average of 65%. At longer term follow-up, parents reported a 78% decrease in symptoms. All other evaluated symptoms (e.g., anxiety, anorexia, behavioral regression, depressed mood) also showed substantial improvement, with some of the most worrisome decreasing to negligible levels. There was no correlation between symptom duration and TPA response. Transient adverse effects ranged from tingling lips to vasovagal reactions, but none were severe. Two subjects experienced bleeding at the central line site.

Discussion: Results of the present study support TPA as a safe and effective treatment for PANDAS in young patients. However, because TPA is an invasive procedure, it should be reserved for severely affected patients.

Latimer M, L'Etoile N, Seidlitz J, Swedo S: Therapeutic plasma apheresis as a treatment for 35 severely ill children and adolescents with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (1):70–75. From Georgetown University School of Medicine, Washington, DC; and other institutions. **The authors declared no conflicts of interest.**

Reference Guide

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CHILD & ADOLESCENT PSYCHIATRY ALERTS

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School-Based Intervention for Disruptive Behavior

Behavior problems in school are often marked by hostility, defiance, and noncompliance with authority. To be problematic, they need not meet diagnostic criteria for a disruptive behavior disorder. Increasingly, schools are recognizing the need to deal with these disruptive behaviors in the classroom setting. Clinical practice guidelines for disruptive behavior disorders are useful in outpatient clinical practice but provide little guidance for school-based programs.

Assessment of possible comorbidities as well as environmental factors should be conducted as part of the treatment-selection process. Evidence-based treatment models for disruptive behavior include behavior management; therapy or counseling; cognitive behavior/social competence training; academic services; separate schools; multimodal programs; and peer mediation. Generally, effect sizes for these approaches are similar; one-to-one interventions are only marginally superior to group interventions; and programs directly targeting aggressive behavior are not significantly more effective than those that are more indirect. Numerous factors determine effectiveness; fidelity to treatment method may be the most critical.

Kuhn T, Ebert J, Gracey K, Chapman G, et al: Evidence-based interventions for adolescents with disruptive behaviors in school-based settings. *Child and Adolescent Psychiatric Clinics of North America* 2015;24 (April):305–317. From Vanderbilt University, Nashville, TN. **Source of funding not stated.**

Attachment-Based Family Therapy for Depression

According to a review, attachment-based family therapy (ABFT) is a promising empirically supported intervention for adolescents with depression and suicide risk as well as their families.

Depression and significant suicidal ideation in teens has been shown to be highly treatment resistant. ABFT has its theoretical foundation in attachment theory. The premise is that adolescents have a basic evolutionary instinct to seek out parents for care and protection. Attachment-promoting parenting is responsive, emotionally attuned, and developmentally flexible. Parenting that is rejecting, intrusive, emotionally unresponsive, or inconsistent puts the child at risk for insecure attachment, which in turn predicts a range of maladaptive outcomes including depression and suicide risk.

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ABFT aims to target important attachment processes in order to improve security and self-perception/ self-efficacy in the adolescent and caregiving efficacy in parents. This is accomplished through 5 tasks completed over 12–16 weeks, or longer if necessary.

Task 1—The Relational Reframe: Initially the problem is reframed, shifting focus away from the adolescent as "the problem" to enhancing family dynamics as part of the solution. Both adolescents and parents agree to participate in relational-focused therapy.

Task 2—Adolescent Alliance: The therapist bonds with the adolescent, increases the patient's awareness of relational ruptures with the parent and their impact, raises feelings of entitlement and expectation of care, and prepares the adolescent to talk with the parents about feelings.

Task 3—Parent Alliance: With the parents, the therapist reinvigorates motivation for caregiving; explores strengths, their own early attachment experiences, and contributing stressors; and teaches task-specific parenting skills.

Task 4—Repairing Attachment: After the goals of tasks 2 and 3 are individually met, the adolescent and their parents rejoin to practice new interpersonal skills. Sessions focus on adolescents' honest but emotionally-regulated disclosure of experiences and feelings they believe have violated the attachment bond. Parents are encouraged to use emotion-coaching skills learned in task 3. These sessions aim to restructure adolescents' negative schemas of self and alter their perception of their parents to see them as caring and available to help. They also provide opportunities to practice managing negative affect, promoting appropriate emotional expression, and tolerating conflict. Task 4 serves as a corrective attachment experience.

Task 5—Promoting Autonomy: The final task, which can take up to half of the therapy sessions, focuses on addressing the adolescent's problems in other areas, such as school and social life, with the parents' support and guidance. Furthering communication and negotiation between adolescent and parents, rather than behavioral management, is the goal of this task. Task 5 sessions serve as opportunities for the family to practice newly-developed respectful and regulated interpersonal problem-solving strategies.

To date ABFT has been investigated in a limited number of studies, all conducted by the same group of investigators, including an author of this review, and only in tightly controlled protocols with highly trained and supervised therapists. ABFT has been compared with a wait-list condition and with enhanced treatment as usual; it produced significant reductions in depressive symptoms. In 1 study, ABFT was superior to enhanced usual care in reducing suicidal ideation, with a large effect size* of 0.97. Benefits were maintained at follow-up 12 weeks after the end of treatment. In an early feasibility study, ABFT was effective when delivered by community-based therapists. ABFT also reduced depressive symptoms and suicidal ideation in an uncontrolled study in 10 openly gay or lesbian young people experiencing suicidality. The effectiveness of ABFT in community-based nonacademic settings has not been established. However, an ongoing, 5-year, NIMH-funded, randomized trial of ABFT, using Family-Enhanced Non-directive Supportive Therapy as an active comparator, will address some of the unanswered questions.

Ewing E, Diamond G, Levy S: Attachment-based family therapy for depressed and suicidal adolescents: theory, clinical model and empirical support. *Attachment and Human Development* 2015; doi 10.1080/14616734.2015.1006384. From Drexel University, Philadelphia, PA. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

***See Reference Guide.**

Olanzapine–Fluoxetine for Bipolar Depression

In a manufacturer-sponsored, randomized controlled trial, the combination of olanzapine and fluoxetine (OFC) was an effective treatment for acute bipolar depression in older children and adolescents. OFC was associated with metabolic and weight effects similar to those seen in adult patient populations.

Background: There are currently 3 medications approved for the treatment of bipolar depression in adults: OFC, quetiapine, and lurasidone. All are under investigation in children and adolescents. The components of OFC have been evaluated in patients aged <18 years for other indications and are FDA approved. Quetiapine has failed to show efficacy in 2 pediatric trials, and results with lurasidone are pending.

Methods: The study was conducted at the request of the FDA and carried out at 41 centers in the U.S., Mexico, and Russia. Participants were aged 10–17 years, met DSM-IV-TR criteria for a current depressive episode of bipolar I disorder, and had few or no manic symptoms. After a taper of all other psychotropic medications, patients were randomly assigned in a 2:1 ratio to receive OFC or placebo for up to 8 weeks. OFC was administered in a forced titration of the 4 available doses, with a maximum permitted dose of 12 mg olanzapine–50 mg fluoxetine. The primary efficacy outcome was the mean change from baseline on the Children's Depression Rating Scale, Revised (CDRS-R). Response was defined as a ≥50% reduction in the CDRS-R and a Young Mania Rating Scale (YMRS) item 1 (elevated mood) score of <2. Remission was defined as a CDRS-R score of ≤28, a YMRS total score of <8, and a Clinical Global Impression-Bipolar overall severity score of ≤3.

Results: A total of 255 patients were included in the intent-to-treat analysis: 170 in the OFC group, and 85 in the placebo group. A total of 15% of participants were aged 10–12 years, and 12 were inpatients at some point during treatment. The average dosage of active medication was 8 mg/day olanzapine and 38 mg/day fluoxetine; 39% of patients received the maximum dose.

Despite a large placebo response, OFC was associated with a significantly greater reduction in the CDRS-R total score (see table), with an effect size* of 0.46. OFC was also associated with more frequent and earlier response and remission than placebo. OFC was superior to placebo for all secondary measures of antidepressant efficacy. Two patients in the OFC group and none in the placebo group experienced emergent mania during treatment.

Antidepressant efficacy measures from baseline to 8 weeks

	OFC (n=170)	Placebo (n=85)	P value for between-group comparison
Change in CDRS-R score	-28.4	-23.4	p=0.003
Response rate	78%	59%	p=0.003
Remission rate	59%	43%	p=0.035

Overall rates of treatment discontinuation were similar in the 2 groups. However, OFC was twice as likely as placebo to be discontinued because of adverse events (14% vs. 6%, respectively). Weight gain, appetite increase, somnolence, tremor, and sedation were all reported more frequently with OFC. A total of 52% of patients receiving OFC and 4% of the placebo group gained >7% of their baseline weight. OFC was also associated with average increases

in total cholesterol, LDL cholesterol, triglycerides, liver enzymes, and prolactin. Mean increases in heart rate and QTc interval were also greater with OFC than placebo.

Discussion: Results of the present study suggest that OFC may be an important option when rapid symptom improvement is required. For greater flexibility, clinicians may prefer separate administration and dosing of the 2 component drugs.

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

Detke H, DelBello M, Landry J, Usher R: Olanzapine/fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 2015;54 (March):217–224. From Eli Lilly and Co., Indianapolis, IN; and the University of Cincinnati College of Medicine, OH. **Funded by Eli Lilly and Co. All study authors declared financial relationships with commercial sources, including Eli Lilly and Co.**

Drug Trade Names*: fluoxetine—*Prozac*; lurasidone—*Latuda*; olanzapine—*Zyprexa*; olanzapine-fluoxetine (OFC)—*Symbyax*; quetiapine—*Seroquel

***See Reference Guide.**

National Suicide Trends

Suffocation, including hanging, continues to increase as a means of suicide for young people in the U.S., according to a CDC analysis of longitudinal data. The high lethality rate of attempted suicide by suffocation underscores the importance of suicide prevention efforts.

National Vital Statistics System data on annual suicide counts were analyzed for young persons aged 10–24 years from 1994, the year when suicide rates peaked in this age group, until 2012. Overall age-adjusted suicide rates fluctuated somewhat during those years but were consistently higher in males than females—e.g., in 2012, the rates were 11.9 and 3.2 per 100,000, respectively. Throughout the study period, firearms were the leading mechanism of suicide in males, but in 2001 suffocation surpassed firearms as the leading mechanism in females. In general, rates of firearm suicides decreased over the years spanned by the analysis, while suffocation rates increased by 6.7% annually in females and 2.2% annually in males. Suicide by suffocation increased in all age groups (10–14 years, 15–19 years, and 20–24 years), all ethnic groups, and all regions of the country. Poisoning, the third leading method, was markedly less common than either firearms or suffocation.

These trends are concerning because suicide attempts by suffocation are lethal an estimated 69–84% of the time, similar to firearms (81%) and much greater than poisoning (2%). The increased use and high lethality of suffocation point out the need to offer effective suicide prevention and to address contagion from media reports of suicides that provide details about suicide methods.

Sullivan E, Annest J, Simon T, Luo F, et al: Suicide trends among persons aged 10–24 years—United States, 1994–2012. *Morbidity and Mortality Weekly Report* 2015;64 (March 6):201–205. From the National Center for Injury Prevention and Control, CDC.

Parent Interventions for Preschool ADHD

Behavioral interventions for parents have strong positive effects in preschool children with ADHD, according to results of a meta-analysis.

Background: An estimated 2–6% of preschool children have ADHD. These children have impairments including academic difficulties, negative parent relationships, and poor social interactions; and they often do not outgrow their symptoms. Evidence, although relatively sparse, suggests that stimulants are an effective treatment for ADHD in preschoolers, but the adverse effects of these agents may be of greater concern than in older children.

Methods: The meta-analysis included all available, published, randomized, controlled trials of behavioral interventions for ADHD in children aged <6 years. Studies were required to use a control condition that was known or hypothesized to be ineffective for ADHD and to report results using an ADHD rating scale. Effect size* was reported as the standard mean difference between treatment groups.

Results: A total of 8 studies (399 participants) were included in the analysis. Active treatments included the Incredible Years Child and Parent Training Programs, Parent–Child Interaction Therapy, the Revised New Forest Parenting Programme, and others including a multicomponent parent training program and a school consultation program. Control conditions were a wait list in 7 studies and community treatment in 1.

The meta-analysis showed a significant benefit of behavioral interventions for parents, with effect sizes ranging from 0.40 to 1.82 (mean, 0.61; $p<0.001$). The studies were highly heterogeneous, but there was no evidence of publication bias. The success of parent training programs was not influenced by the average age of children in the study, the duration of treatment, or involvement of the child in the training. The sample size was too small to permit investigation of secondary research questions.

Discussion: The effect size for parent training shown by this meta-analysis is larger than effect sizes that have been reported for all but the highest doses of stimulant medications. The mean age of children in the 8 studies ranged from 3 to 5 years. Training was beneficial for children as young as 3 years, an age when parents may be particularly hesitant to use medication.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis, but individual study quality was not assessed.

Mulqueen J, Bartley C, Bloch M: Meta-analysis: parental interventions for preschool ADHD. *Journal of Attention Disorders* 2015;19 (February):118–124. From Yale University School of Medicine, New Haven, CT. **Funded by the NIH; and other sources. The authors declared no conflicts of interest.**

***See Reference Guide.**

Topiramate and Eating Disorders

A small case series highlights the need for careful monitoring for eating-disorder symptoms in adolescents receiving topiramate for migraine prevention.

Topiramate is the first medication FDA approved for migraine prevention in adolescents. Appetite suppression is a well-known adverse effect of topiramate. Weight loss, even in patients with no history of an eating disorder, can lead to behavioral, cognitive, and physical symptoms typical of eating disorders.

Charts from the Mayo Clinic Eating Disorders Program were retrospectively reviewed for 7 adolescent girls, aged 13–18 years, who received topiramate treatment between 2008 and 2013. Although topiramate is also indicated for seizure control, all 7 girls were taking the drug for migraine or chronic headache. Eating-disorder diagnoses were bulimia nervosa (n=1), anorexia nervosa (n=2), and eating disorder not otherwise specified (n=4). The primary eating-disorder symptom was dietary restriction in all patients. Five girls also reported self-induced vomiting, 3 reported binge eating, and 1 reported laxative abuse. One patient had a history of eating disorder not otherwise specified that had been in remission before topiramate initiation, 3 reported symptom onset after starting topiramate, and 3 estimated the eating-disorder symptoms preceded topiramate use, although none had an eating-disorder diagnosis. Six of the 7 patients experienced weight loss ranging from 11 to 50 lbs. A single patient gained a >70 lbs. as a result of binge eating.

The retrospective nature of the study does not allow for conclusions regarding the direction or causality of the association between topiramate and eating disorders. However, these cases suggest that prescribers should be aware of the potential for topiramate to trigger or exacerbate eating-disorder symptoms in adolescents. Patients with or at risk for developing an eating disorder should be monitored carefully after topiramate initiation, and weight loss should not be dismissed as an adverse effect of medication. Further study to determine the prevalence of and risk factors for eating-disorder symptoms in adolescents taking topiramate appears to be warranted.

Lebow J, Chuy J, Cedermark K, Cook K, et al: The development or exacerbation of eating disorder symptoms after topiramate initiation. *Pediatrics* 2015; doi 10.1542/peds.2014-3413. From Mayo Clinic College of Medicine, Rochester, MN; and the University of Miami, FL. **This study was conducted with no external funding. The authors declared no conflicts of interest.**

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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.

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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Generic *Abilify* Approved

The first generic version of *Abilify* (aripiprazole) has received FDA approval for the treatment of bipolar disorder and schizophrenia. Generics will be marketed by several manufacturers and will carry the same Boxed Warnings regarding the risk of suicidal behavior and thinking in children, adolescents, and young adults, and increased risk of death with off-label use in elderly patients with dementia-related psychosis.

FDA News Release: FDA approves first generic Abilify to treat mental illness. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

New Extended-Release Methylphenidate

A new formulation of extended-release methylphenidate showed dose-related efficacy in a phase III clinical multicenter trial in patients with ADHD. The formulation, methylphenidate hydrochloride extended-release (MPH-MLR; *Aptensio XR*), has a novel two-peak release profile.

Background: MPH-MLR incorporates multilayer beads, with 37% of the labeled dose available as immediate-release and the rest as extended-release. Previous research indicates the methylphenidate concentration reaches its first peak within about 2 hours post-dose, followed by a modest decline at about 5 hours, and then a second peak at approximately 7 hours.

Methods: This multicenter U.S. trial was conducted in 230 children and adolescents, aged 6–18 years (mean age, 11 years; 67% boys), with a confirmed diagnosis of ADHD (DSM-IV-TR). Following a screening phase during which previous ADHD medications were discontinued, patients were randomly assigned to receive 1 of 4 different doses of MPH-MLR (10, 15, 20, or 40 mg) or placebo in a double-blind fashion. After 1 week of double-blind treatment, all patients had the option of receiving open-label MPH-MLR, flexibly dosed, for 11 weeks. The primary efficacy endpoint was change from baseline to the end of the double-blind period in the ADHD Rating Scale-IV (ADHD-RS-IV) total score.

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Results: After 1 week, there was a statistically significant difference among treatments in the primary efficacy analysis (p=0.004). In a secondary analysis, all dosages were associated with a greater decrease in the ADHD-RS-IV total score than placebo, but the difference was only statistically significant for the 2 higher doses, 20 mg (p=0.01) and 40 mg (p=0.001). The 2 higher doses were associated with significant decreases in both the hyperactivity and inattention subscales of the ADHD-RS-IV.

ADHD-RS-IV scores continued to decline throughout the open-label phase in the 200 patients who continued treatment. Mean scores decreased from 36 at baseline to 13.5 at week 12. The most frequent adverse events during open-label treatment were decreased appetite (19%), headache (18%), and insomnia (12%). Two patients experienced serious adverse events that were related to study treatment: aggression and mood swings. There were no unexpected adverse events beyond those known for this class of medication.

Discussion: Only about 3.5% of patients received the 2 lowest doses of MPH-MLR during the open-label dose-optimization phase. However, these lower doses may be useful for gradual dose titration in the clinical setting. Although it is impossible to compare directly MPH-MLR with other extended-release formulations of methylphenidate, treatment effects on the ADHD-RS-IV at the end of the open-label study phase are in line with other drugs in this class.

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

Wigal S, Nordbrock E, Adjei A, Childress A, et al: Efficacy of methylphenidate hydrochloride extended-release capsules (Aptensio XRTM) in children and adolescents with attention-deficit/hyperactivity disorder: a phase III, randomized, double-blind study. *CNS Drugs* 2015; doi 10.1007/s40263-015-0241-3. From AVIDA, Inc., Newport Beach, CA; Rhodes Pharmaceuticals, L.P., Coventry, RI; and other institutions. **Funded by Rhodes Pharmaceuticals, L.P. All study authors disclosed financial relationships with commercial sources, including 5 of the 6 with Rhodes Pharmaceuticals.**

***See Reference Guide.**

DBT in Adolescent Bipolar Disorder

Dialectical behavior therapy, used adjunctively with medication, showed promise in treating bipolar disorder in adolescents, including some with past suicide attempts or nonsuicidal self-injury.[1] The study established the feasibility of conducting a randomized trial in this patient population, but the number of enrolled patients was too small for valid statistical comparison of many study outcomes. The results suggest that the DBT focus on commitment to treatment may have enhanced participation.

Methods: These study authors, working within a specialty clinic for child and adolescent bipolar disorder, previously conducted open development studies of a manualized program of DBT with Suicidal Adolescents.[2] Building on that experience, they offered randomly assigned DBT or treatment as usual to adolescents, aged 12–18 years, with bipolar I, II, or NOS disorders and an acute manic, mixed, or depressive episode within the prior 3 months. Patients were assigned in a 2:1 ratio to DBT or community treatment. All patients received guideline-based pharmacotherapy. DBT consisted of group skills training with family participation, individualized DBT, skills coaching by telephone, and weekly consultation among therapists. Treatment sessions were scheduled weekly for the first 6 months and then tapered during the second 6 months, for a total of 36 sessions. The comparison group received eclectic standard-of-care psychotherapy from specialist therapists at the clinic. Outcomes were assessed quarterly by a rater blind to treatment assignment.

Results: Of 26 families approached for the study, 2 declined all participation, 2 met exclusion criteria, and 2 more were found eligible but withdrew before attending any sessions. The final sample consisted of 14 adolescents who received DBT and 6 who had treatment as usual. In the DBT group, participants had an average of 1 past suicide attempt (maximum, 5). Five patients

had a history of nonsuicidal self-injury, compared with no suicide attempts and 1 with self-injury in the comparison group. Those who received DBT participated in an average of 30 sessions, compared with about 9 sessions in the treatment-as-usual group.

Adolescents and parents in both groups reported high levels of satisfaction with treatment, the adolescent's progress, the length of treatment, and the frequency of therapy sessions.

Over the treatment year, adolescents who received DBT had less severe depressive symptoms than the control group on the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children Depression Rating Scale (p=0.05; effect size,* 0.98). For other study outcomes, differences favored DBT but did not differ statistically from treatment as usual. However, within-group change from baseline in some outcomes was statistically significant with DBT but not treatment as usual. Improvements in manic and depressive symptoms and emotional dysregulation; weeks free of depression; weeks free of mania or hypomania; and euthymic weeks were greater in the DBT group. Scores on the Suicidal Ideation Questionnaire–Junior decreased over the study year in 83% of the DBT group and were unchanged in the rest, while suicidal ideation increased in half of the treatment-as-usual group. There were 2 suicide attempts during treatment in the DBT group and none in the control group.

[1]Goldstein T, Fersch-Podrat R, Rivera M, et al: Dialectical behavior therapy for adolescents with bipolar disorder: results from a pilot randomized trial. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (March):140–149. From the University of Pittsburgh Medical Center, PA; and Nationwide Children's Hospital, Columbus, OH. **Funded by the NIMH.**

[2]Miller A, Rathus J, Lineham M: *Dialectical Behavior Therapy with Suicidal Adolescents*. New York: Guilford Press; 2006.

***See Reference Guide.**

ECT in Adolescents with Resistant Depression

A 2004 guideline from the American Academy of Child and Adolescent Psychiatry requires 3 criteria for use of ECT in adolescent depression: a diagnosis of indication, persistent and disabling symptoms, and non-responsiveness to 2 medication trials. Reported response rates for ECT range from 75% to 100% in adolescents with mood disorders. Despite the guideline and a small amount of evidence, use of ECT in adolescents remains controversial and little research on ECT in this patient population has been conducted in the past decade; there appear to be only 10 publications, all of which were case reports or case series. The aim of the present study was to provide details on ECT for depression in a comprehensive sample of adolescents.

Investigators reviewed charts of all patients aged <19 years who received ECT at a tertiary psychiatric hospital in 2008–13. ECT parameters depended partially on illness severity. In patients without an urgent need for response, twice-weekly administration, unilateral placement, and ultra-brief pulse width was preferred. In patients who were acutely suicidal, more severely ill, or unresponsive to other treatments, thrice-weekly ECT, bitemporal placement, and brief pulse width was preferred.

ECT was administered to 13 adolescents (mean age, nearly 17 years; range, 15–18 years). The patients had previously undergone a mean of 6 adequate treatment trials (range, 3–11). In this study, they received an average of 14 ECT sessions, of which 12.5 resulted in adequate seizures. Unilateral electrode placement was used in 8 patients, of whom 5 were switched to bilateral placement. Bifrontal placement was used in 4 adolescents and bitemporal in 8.

Treatment response was measured with the Beck Depression Inventory-II (BDI-II) self-report, with reliable improvement defined as a ≥10-point reduction in score. A total of 10 patients (77%) experienced reliable improvement, and 3 (23%) had full recovery (BDI-II total score <11).

According to a multivariate predictive model, for every ECT session there was a nearly 1-point reduction in BDI-II score. Although not systematically evaluated, presence of borderline symptoms, drug use, and high levels of anxiety did not appear to affect ECT outcomes. There were 4 relapses over 6 months of follow-up among the 8 patients who had experienced reliable improvement with ECT, suggesting a possible need for continuation ECT in these severely impaired patients.

Cognitive impairment was measured with the clinician-administered Montreal Cognitive Assessment (MoCA) at baseline, after every sixth treatment on average, and upon ECT completion. Cognitive impairment was mild in 9 of the 13 patients and moderate in 2. Two patients continued to have subjective memory impairment at 2- and 6-month follow-up. Two study patients experienced no cognitive impairment. There was no statistical relationship of MoCA scores to the number of treatments. Other adverse effects were headache in 10 patients, musculoskeletal pain in 9, nausea and vomiting in 3, and prolonged seizure in 3. All events were transient and responsive to symptomatic or preventive measures.

Zhand N, Courtney D, Flament M: Use of electroconvulsive therapy in adolescents with treatment-resistant depressive disorders: a case series. *Journal of ECT* 2015; doi 10.1097/YCT.0000000000000236. From the University of Ottawa, Canada; and other institutions. **Funded by the Institute of Mental Health Research, Ottawa, Canada; and other sources. The authors declared no conflicts of interest.**

Duloxetine for Generalized Anxiety Disorder

In a phase III clinical trial, duloxetine (*Cymbalta*) was superior to placebo in treating generalized anxiety disorder (GAD) in children and adolescents.

Methods: Study participants were patients, aged 7–17 years, who met DSM-IV-TR criteria for GAD and had symptom scores on the Pediatric Anxiety Rating Scale (PARS) indicating general anxiety symptoms of at least moderate severity and significant social, academic, and/or family dysfunction. Patients were randomly assigned to receive double-blind, flexibly-dosed duloxetine at 30–120 mg/day or placebo for 10 weeks. All patients were offered open-label duloxetine for an additional 18 weeks. Patients receiving psychotherapy before enrollment were allowed to continue. The primary efficacy outcome measure was the GAD-specific subset of symptoms from the PARS symptom checklist.

Results: A total of 272 patients were randomly assigned to duloxetine or placebo. Of these, 210 completed the acute phase and continued to extension treatment, and 160 completed the extension phase. More than half of the patients did not have a diagnosis of GAD before recruitment for this study, and the mean time since the first appearance of distressing or impairing anxiety symptoms was >4 years.

At 10 weeks, duloxetine was associated with greater improvement in anxiety symptoms than placebo (effect size,* 0.5; $p<0.001$). Duloxetine was associated with a higher rate of response (≥50% improvement in PARS GAD score) compared with placebo: 59% vs. 42% ($p\leq0.05$). Remission (PARS score ≤8) was also more frequent with duloxetine than placebo (50% vs. 34%; $p\leq0.05$). Improvement and remission measured with the Clinical Global Impression–Severity* scale were also greater with duloxetine treatment, as was functional remission, measured with the Children's Global Assessment Scale.

Treatment-related adverse events were similar to those reported with duloxetine in adults and in other pediatric populations. There were no differences between duloxetine and placebo in suicidal ideation or behavior or nonsuicidal self-injury. During acute treatment, 8 patients who received duloxetine and 7 who received placebo had emergent suicidal ideation; 6 patients had treatment-emergent suicidal ideation during the extension phase.

Discussion: This study suggests a moderate effect size for duloxetine in treating GAD, consistent with the results of other studies of antidepressants in young people with anxiety disorders unrelated to obsessive-compulsive disorder.

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

Strawn J, Prakash A, Zhang Q, Pangallo B, et al: A randomized, placebo-controlled study of duloxetine for the treatment of children and adolescents with generalized anxiety disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 2015;54 (April):283–293. From the University of Cincinnati, OH; and other institutions including Eli Lilly and Co., Indianapolis, IN. **Funded by Eli Lilly and Company. All study authors disclosed financial relationships with commercial sources, including Eli Lilly.**

***See Reference Guide.**

Pediatric Pill-Swallowing Interventions

Inability to swallow pills is a common pediatric problem that can be an important barrier to treatment, but there has been very little research on effective techniques to improve pill swallowing. The limited evidence indicates that several different approaches are effective.

Methods: A PubMed search identified all English-language studies published since 1987 that were conducted in patients, aged 0–21 years, with pill-swallowing difficulties not attributable to dysphagia or conditions such as severe developmental disability.

Results: The 5 identified studies included 4 cohort studies and 1 case series; no randomized trials were identified. Sample sizes ranged from 11 to 67. Two studies were limited to children aged ≤13 years, 2 also included adolescents up to age 17 years, and 1 included patients as old as 21 years. A behavioral intervention that included shaping and modeling was used in 2 studies. The remaining 3 studies evaluated the effects of: swallowing instructions, a flavored spray that lubricated the mouth and tongue, and an education intervention that included information about the esophagus, 5 different head positions to try, and reassurance.

In all of the studies, most or nearly all patients learned to swallow pills, usually after only 1 practice session. Continued ability to swallow pills was demonstrated in 1 study of patients with HIV at 3- and 6-month follow-up using pill counts, CD4+ T-cell percentage, and viral load. Two other studies assessed ongoing compliance with telephone calls or other methods.

Discussion: The present review identified a number of methods that clinicians can use to facilitate pill-swallowing skills. Children as young as 2 years were helped; in fact, younger children needed less training than older ones, perhaps because they had fewer previous negative experiences.

Patel A, Jacobsen L, Jhaveri R, Bradford K: Effectiveness of pediatric pill swallowing interventions: a systematic review. *Pediatrics* 2015;135 (May):883–889. From the University of North Carolina School of Medicine, Chapel Hill; and other institutions. **This study was conducted without external funding. The study authors declared no conflicts of interest.**

Predicting Persistence of Nonsuicidal Self-Injury

In a longitudinal study of adolescents hospitalized for suicide risk, those with nonsuicidal self-injury (NSSI) who were motivated by automatic positive reinforcement—the desire to feel something, even if it is pain—were the most likely to continue engaging in NSSI 6 months later.

Background: NSSI has been conceptualized as having 4 different functions or motivations: automatic positive reinforcement, automatic negative reinforcement (the most commonly reported, consisting of removal of an aversive stimulus), and 2 less common functions involving other people: social negative reinforcement (avoidance) and social positive reinforcement (to gain attention). Automatic positive reinforcement is believed to be a more common motivator of NSSI in patients with depression or PTSD, possibly to compensate for feelings of emptiness, anhedonia, or a restricted range of affect.

Methods: Study participants were adolescents (mean age, 15 years; 64% girls) who received treatment at an inpatient psychiatric unit because of suicide attempts, ideation, or self-injury with suicidal ideation. Patients and their parents were interviewed at baseline and again at 6 months after discharge. NSSI was assessed with the Functional Assessment of Self-Mutilation (FASM) questionnaire, which captures the frequency of NSSI and the 4 functional subscales of perceived reasons for the behavior.

Results: Of the 92 patients with both baseline and follow-up data, 71 (77%) reported NSSI at baseline. At 6-month follow-up, 40 (56%) of these patients continued to report NSSI. Young people who stopped NSSI were more likely than those who continued to have major depressive disorder and/or a substance use disorder at baseline. High baseline scores on automatic positive reinforcement were predictive of continued NSSI (odds ratio,* 1.90; p=0.03). Continued NSSI was not predicted by any demographic factors, past history of abuse, other concomitant psychiatric disorders, or the other 3 NSSI subscales.

The prevalence of moderate-to-severe depression was assessed weekly during the 26-week follow-up. In a multivariate model, patients who were experiencing moderate-to-severe depression >50% of the time had a significantly increased risk of continued NSSI (odds ratio, 3.32; p=0.02), while the association with automatic positive reinforcement was undiminished.

Discussion: The results of this longitudinal study suggest that it is important to assess patients' reasons for NSSI and provide targeted treatment for the different motivations. For automatic positive reinforcement, mindfulness-based therapies that target emptiness and dissociative-like states can be helpful. For both types of automatic reinforcement, it seems critical to focus on emotion monitoring and positive alternatives to self-injury. The apparently conflicting results with depression suggest that acute and chronic depression may have differential effects on the persistence of NSSI.

Yen S, Kuehn K, Melvin C, Weinstock L, et al: Predicting persistence of nonsuicidal self-injury in suicidal adolescents. *Suicide and Life-Threatening Behavior* 2015; doi 10.1111/sltb.12167. From Brown University, Providence, RI; and other institutions. **Funded by the NIMH. The authors did not include disclosure of potential conflicts of interest.**

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Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

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.

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 are posted at www.alertpubs.com.

CHILD & ADOLESCENT PSYCHIATRY ALERTS

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Stimulants: Comparative Effects on Functional Outcomes

In a head-to-head comparison, lisdexamfetamine was associated with a modestly larger effect on function than atomoxetine in children and adolescents with ADHD who had previously experienced inadequate response to methylphenidate.[1]

Methods: The multinational clinical trial was conducted in children and adolescents, aged 6–17 years, with a primary diagnosis of ADHD who had at least moderately severe symptoms and were experiencing (or had experienced) an inadequate response to methylphenidate. After a 7-day washout of previous medications, patients received treatment for 9 weeks with double-blind, randomly assigned, flexible-dose atomoxetine or lisdexamfetamine. The primary efficacy and safety outcomes of the study have been published previously.[2] The present report describes the secondary endpoint of functional impairment, which was measured using the ADHD-specific Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P). The scale comprises 50 items, divided into 6 domains: family; learning/school; life skills; child's self-concept; social activities; and risky activities. Each item is scored on a 4-point Likert scale, where 0=never or not at all, and 3=very often or very much. The developers of this scale recommend using half of 1 standard deviation as a cutoff for a clinically meaningful difference.

Results: A total of 262 patients were included in the full analysis set. About three-fourths were children (aged 6–12 years). Baseline scores on the WFIRS-P indicated the greatest degree of functional impairment in the family and learning/school domains.

At 9 weeks, both treatments were associated with large improvements in the WFIRS-P total score ($p<0.001$ for both drugs). There were also significant improvements in all 6 domains, with the largest improvement observed in learning/school. In both treatment groups, the improvement from baseline in the total score was in the clinically meaningful range. Clinically meaningful improvement occurred with both drugs in the domains of learning/school and life skills and in the family domain with lisdexamfetamine.

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Compared with atomoxetine, lisdexamfetamine was associated with numerically greater decreases in WFIRS-P total score and in all domains except life skills. The differences were statistically significant for the total score (p=0.046; effect size,* 0.27) and for learning/school (p=0.002; effect size, 0.43) and social activities (p=0.014; effect size, 0.34).

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

[1]Nagy P, Hage A, Coghill D, Caballero B, et al: Functional outcomes from a head-to-head, randomized, double-blind trial of lisdexamfetamine dimesylate and atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder and an inadequate response to methylphenidate. *European Child and Adolescent Psychiatry* 2015; doi 10.1007/s00787-015-0718-0. From Vadaskert Child and Adolescent Psychiatry Hospital and Outpatient Clinic, Budapest, Hungary; and other institutions including Shire, Eysins, Switzerland and Wayne, PA. **Funded by Shire Development LLC. All study authors disclosed financial relationships with commercial sources including Shire.**

[2]Dittmann R, et al: Efficacy and safety of lisdexamfetamine dimesylate and atomoxetine in the treatment of attention-deficit/hyperactivity disorder, a head-to-head, randomized, double-blind, phase IIIb study. *CNS Drugs* 2013;27:1081–1092. See *Child & Adolescent Psychiatry Alerts* 2013;15 (October):59–60.

Drug Trade Names*: atomoxetine—*Strattera*; lisdexamfetamine—*Vyvanse*; methylphenidate—*Ritalin

***See Reference Guide.**

Parent Management Training for ADHD/Conduct Problems

In an observational study, parent management training produced positive effects on children with conduct problems, regardless of whether or not they had comorbid ADHD.

Background: Meta-analyses have shown that parent management training is effective for children with conduct problems or ADHD. There are limited data on its efficacy in children with the combined diagnosis, which has been suggested to represent a distinctive, treatment-resistant pattern of dysfunction.

Methods: This naturalistic study was conducted in 253 children, aged <12 years, and their families. Parents received parent management training, Oregon model (PMTO), provided by Norwegian mental health agencies or welfare services. PMTO is a manualized program designed to enhance specific parenting skills: skill encouragement; monitoring/supervision; problem solving; positive involvement; and limit setting/discipline. Participants typically require 20–50 sessions to reach treatment goals. Child outcomes were assessed using both parent- and teacher-rated variables after parents completed PMTO. Assessments included the parent-rated Child Behavior Checklist, Parent Daily Report, and Social Skills Rating System (SSRS), as well as the teacher-rated SSRS and Teacher Report Form.

Results: Of the 253 children enrolled, 97 (38%) had comorbid ADHD. Participants were a mean age of about 8.5 years, 73% were boys, the average family income level was "lower to middle," and 35% were children of single parents. Parents participated in an average of 24 PMTO sessions.

At baseline, the children with ADHD scored higher than those without the diagnosis on parent and teacher ratings of attention problems, externalizing problems, and social problems. Teachers also rated these children as more impaired socially and academically. There were no differences between groups with and without ADHD in child age, family income, parent age and education, number of siblings, single-parent status, or whether the family received welfare.

The diagnosis of ADHD was predictive of only 1 of the 14 outcome variables, and this association was only marginal: Children with ADHD received lower parent ratings on social skills after treatment. After parent completion of PMTO, children with ADHD still scored more poorly than their peers on teacher- and parent-reported attention problems and social competence, but other differences present at baseline were no longer apparent. Among children with ADHD, 36% were no longer in the clinical range for parent-reported externalizing problems, compared

with 30% of the non-ADHD group. A total of 16% of both groups were no longer in the clinical range for teacher-rated externalizing problems. Children with ADHD did less well if their families were affected by maternal anxiety/depression and/or by low income.

Discussion: Results of this study suggest that children with conduct problems and ADHD can benefit from parent management training and that therapy should be adjusted to address contextual factors such as maternal mood or financial challenges.

Bjornebekk G, Kjobli J, Ogden T: Children with conduct problems and co-occurring ADHD: behavioral improvements following parent management training. *Child & Family Behavior Therapy* 2015; doi 10.1080/07317107.2015.1000227. From the University of Oslo, Norway. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

Skeletal Effects of Psychotropic Drugs in Boys

According to results of a longitudinal study, both risperidone (*Risperdal*) and SSRIs are associated with reduced bone mineral density (BMD) in boys.

Background: Loss of bone mass is a potentially serious, but largely neglected, adverse effect of antipsychotics and SSRIs. Possible mechanisms include hyperprolactinemia for antipsychotics and disruption of functional serotonin signaling in bone cells and altered sympathetic nervous system activity for SSRIs.

Methods: Study participants were young patients, aged 7–17 years, who had been receiving treatment with risperidone for any indication for >6 months. Those who were taking additional antipsychotics at baseline were excluded, but concomitant use of other psychotropics was permitted, and about half of patients were also taking an SSRI. Because BMD is strongly affected by gender and there were few girls available at follow-up, the analysis was restricted to the 94 boys who returned for follow-up 18 months after enrollment and who had detectable serum risperidone levels. Daily calcium and vitamin D intake, as well as physical activity, were estimated for the week before study entry. At baseline and follow-up, trabecular BMD was measured at the non-dominant ultradistal radius and the lumbar spine. Markers of bone turnover were measured only at the follow-up visit.

Results: At 18-month follow-up, 70 patients were still taking risperidone and 24 had either stopped taking the drug or switched to another antipsychotic. A total of 44 patients were taking an SSRI at both baseline and follow-up visits, and 37 had no SSRI use at either visit. The most common diagnoses in the study cohort were ADHD (88%) and disruptive behavior disorders (87%); only 4 patients had a diagnosis of depression. Risperidone was prescribed primarily for irritability and aggression.

Compared with patients who discontinued risperidone, those who continued the agent had significantly lower trabecular BMD ($p<0.008$; effect size,* 1.03) and marginally significantly higher lumbar-spine BMD. For both measurements, values remained stable in patients who continued taking risperidone and increased in those who stopped. Prolactin levels were abnormally high at follow-up in half of the risperidone continuation group, compared with none of the discontinuation group. The prolactin concentration at follow-up was significantly associated with lumbar-spine BMD ($p<0.02$), but not with radius trabecular BMD. Bone turnover markers at follow-up did not differ according to risperidone continuation status.

After adjustment for confounding factors, SSRI use was associated with reduced bone mass at the ultradistal radius and lumbar spine at baseline and follow-up ($p<0.05$ for baseline and follow-up measures at both sites). Values remained stable between the 2 visits. SSRI therapy was associated with a marginal decrease in osteocalcin concentration, but no differences in other markers.

Discussion: Although both affect BMD, risperidone and SSRIs appear to be associated with different trajectories of reduction in bone mass. Because age-associated bone loss is directly related to peak BMD achieved by young adulthood, reductions in BMD caused by extended use of these medications in youth may result in an increased risk of osteoporotic fractures later in life.

Calarge C, Burns T, Schlechte J, Zemel B: Longitudinal examination of the skeletal effects of selective serotonin reuptake inhibitors and risperidone in boys. *Journal of Clinical Psychiatry* 2015;76 (May):607–613. From the University of Iowa Carver College of Medicine, Iowa City; and other institutions. **Funded by the National Alliance for Research on Schizophrenia and Depression; and the NIH. The authors declared no conflicts of interest.**

***See Reference Guide.**

Practice Parameter for Eating Disorders

Outpatient psychosocial therapies are the initial treatment of choice for children and adolescents with eating disorders, according to a new practice parameter from the American Academy of Child and Adolescent Psychiatry. Use of pharmacotherapy is supported by scant evidence and is generally not recommended.

The practice parameter offers 7 recommendations.

1. Mental health clinicians should screen all child and adolescent patients for eating disorders by measuring height and weight, asking about eating patterns and body satisfaction, and possibly using a short self-report scale such as the Eating Disorder Examination–Questionnaire. Patients should be referred for further evaluation if there is concern.

2. A positive screening should be followed by a full evaluation, including laboratory studies and bone density imaging as indicated.

3. Severe acute physical signs and medical complications must be treated. Most physical abnormalities are reversible with adequate diet and weight restoration. Guidelines for hospitalization and nasogastric feeding are available from the American Academy of Pediatrics and others.

4. Psychiatric hospitalization, day programs, partial hospitalization programs, and residential programs for eating disorders should only be considered when outpatient interventions have been unsuccessful or are unavailable.

5. Treatment usually requires a multidisciplinary team that is sensitive to the needs, developmentally aware, and skilled in the care of children and adolescents with eating disorders.

6. Outpatient psychosocial interventions (e.g., family-based treatment, adolescent-focused therapy, cognitive-behavioral therapy) are the preferred initial treatment, but are supported by limited evidence.

7. Results with pharmacotherapy have not been encouraging. Antidepressants or atypical antipsychotics may be useful for comorbid conditions or as adjunctive or second-line therapy.

The complete practice parameter, which also includes evidence-based practices for evaluation and detailed information on the 2 new eating disorder diagnoses in DSM-5, is available at www.aacap.org.

Lock J, La Via M, and the American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). *Journal of the American Academy of Child and Adolescent Psychiatry* 2015;54 (May):412–425.

Duloxetine Safety in Children and Adolescents

The safety and tolerability of duloxetine in children and adolescents is similar to that in adults, according to a pooled analysis of data from the manufacturer's phase-III pediatric clinical trials. Up to 36 weeks of follow-up in >400 exposed patients revealed no new safety concerns.

Methods: The analysis included 2 randomized controlled trials of similar design except for the use of fixed-dose duloxetine (30 or 60 mg/day) in 1 and flexibly-dosed duloxetine (60–120 mg/day) in the other. Study participants were children, aged 7–11 years, and adolescents, aged 12–17 years, with major depressive disorder. Each study included a 10-week acute-treatment phase using duloxetine, placebo, or the active comparator fluoxetine. In a subsequent 26-week extended-treatment phase, patients were continued on double-blind active treatment, and those in the placebo group were switched to duloxetine. Suicidal ideation/behavior and nonsuicidal self-injury (NSSI) were assessed throughout the study using the Columbia Suicide Severity Rating Scale. During acute treatment, 341 patients received duloxetine, 234 fluoxetine, and 225 placebo. For the extended phase, 405 patients received duloxetine (237 continued and 168 switched from placebo) and 176 continued fluoxetine.

Results: During the acute phase, treatment-emergent adverse events were reported at a similar rate with the 2 active drugs and placebo (62–63%), both overall and in the subgroups of children and adolescents. The most common acute adverse events with duloxetine were headache and gastrointestinal events. Nausea, diarrhea, and sedation were reported statistically significantly more often with duloxetine than placebo, and nausea and dizziness were statistically more frequent with duloxetine than fluoxetine. The frequency of discontinuation for serious adverse events during acute treatment was higher with duloxetine than fluoxetine or placebo (7, 4, and 1 patient(s), respectively). In the duloxetine group, these events included 2 intentional overdoses, 1 instance of suicidal ideation, and 1 occurrence of self-injurious behavior. During extended treatment, 5 patients taking duloxetine and 3 taking fluoxetine had their treatment discontinued because of serious adverse events.

There were no completed suicides in any treatment group. Rates of new-onset suicidal ideation, suicidal behavior, and NSSI were similar with the 2 active medications and did not differ statistically from placebo. Treatment-emergent suicidal ideation occurred during the entire 36-week study in 11% of the duloxetine group and 15% of the fluoxetine group. A total of 6 patients taking duloxetine (1.8%) and 3 taking fluoxetine (1.3%) exhibited any suicidal behavior. Majorities (≥75%) of patients in each group who had initial suicidal ideation experienced improvement in ideation during acute or extended treatment.

Cardiovascular data, ECG studies, and lab test results did not reveal any new safety concerns with either of the 2 active drugs. Both active medications were associated with weight loss compared with placebo, but this did not translate into reduced gains in height, and most patients recovered their initial weight during extension treatment.

Emslie G, Wells T, Prakash A, Zhang Q, et al: Acute and longer-term safety results from a pooled analysis of duloxetine studies for the treatment of children and adolescents with major depressive disorder. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (May):293–305. From the University of Texas Southwestern and Children's Medical Center, Dallas; and other institutions including Eli Lilly and Company, Indianapolis, IN. **Funded by Eli Lilly and Company. All study authors disclosed potentially relevant financial relationships with commercial sources, including Eli Lilly.**

Drug Trade Names*: duloxetine—*Cymbalta*; fluoxetine—*Prozac

Fluoridated Water and ADHD

According to results of an ecological study, water fluoridation is correlated with prevalence of parent-reported ADHD.

Background: Fluoride is environmentally widespread and has known developmental neurotoxic effects, but it has received little attention as a potential ADHD risk factor. Fluoride can cross the placenta and accumulate in the infant brain, where it may adversely affect levels of neurotransmitters important in learning and memory. Exposure to fluoride in water during childhood has also been associated with impaired attention and cognitive and intellectual functioning. Pathways by which fluoride in the water supply can influence the development

of ADHD are by suppressing thyroid activity and by corroding lead-bearing water pipes, leading to lead ingestion.

Methods: Data on statewide ADHD prevalence was collected from the Centers for Disease Control and Prevention (CDC) whose estimates were derived from the National Survey of Children's Health, conducted in 2003, 2007, and 2011. In this survey, a random sample of parents was asked whether a child (aged 4–17 years) in the household had received an ADHD diagnosis from a health care provider. Estimates of the proportion of people in each state receiving optimally fluoridated water from public supplies in 5 years between 1992 and 2008 were also collected from the CCD. Optimally fluoridated water during those years contained the U.S. recommended level of 0.7–1.2 mg/L. For some years, the CDC distinguished between the proportion of people receiving naturally or artificially fluoridated water.

Results: Median water fluoridation from public water systems increased over time, from 58% in 1992 to 66% in 2008. Overall ADHD prevalence tended to increase over time and was highest in the Southern region of the country and lowest in the West, in parallel with water fluoridation rates. For nearly every pair of health-survey years and fluoridation-prevalence years examined, fluoridation rates were correlated with ADHD prevalence, with significant coefficients (Pearson's r)* ranging from 0.25 to 0.39 ($p \leq 0.05$). When artificial and natural fluoridation were examined separately, only artificial fluoridation was associated with ADHD prevalence.

Because low-income families tend to receive fluoridated public water and to have higher ADHD prevalence, the analysis was adjusted for average statewide family income estimates from the U.S. Census Bureau. In a multivariate analysis, ADHD prevalence in 2003 was independently associated with higher rates of artificial fluoridation in 1992 ($p=0.03$) after adjustment for higher rates of natural fluoridation and higher family income, both of which predicted lower rates of ADHD. After adjusting for income, each 1% increase in the fluoridation rate in 1992 was associated with 67,000 additional ADHD diagnoses in 2003; 93,000 in 2007; and 131,000 in 2011.

Discussion: Results of this study indicate that states in which a higher proportion of people receive fluoridated water also have a higher prevalence of ADHD. However, because of the study design, the association cannot be assumed to be causal. Further study of fluoridated water as a potential risk factor for ADHD appears to be warranted.

Malin A, Till C: Exposure to fluoridated water and attention deficit hyperactivity disorder prevalence among children and adolescents in the United States: an ecological association. *Environmental Health* 2015; doi 10.1186/s12940-015-0003-1. From York University, Toronto, Canada. Source of funding not stated. **The authors declared no conflicts of interest.**

***See Reference Guide.**

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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.

Pearson Correlation Coefficient (r): A measure of the linear correlation between 2 variables. A value of 1 is total positive correlation, 0 is no correlation, and −1 is total negative correlation. An r value >0.75 is generally considered to be relatively strong; correlations between 0.45 and 0.75 are moderate, and those <0.45 are considered weak.

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 are posted at www.alertpubs.com.

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Risperidone vs. Valproic Acid in Preschool Bipolar Disorder

In a small randomized trial, risperidone was clearly superior to placebo in young children with bipolar I disorder, while valproic acid was not. Children were highly sensitive to the adverse effects of both medications, suggesting a need for frequent monitoring.

Methods: The study enrolled 46 patients, aged 3–7 years, with bipolar I disorder, experiencing mixed or manic episode. Patients with comorbid ADHD were included. After a washout of prior medications, including stimulants, patients received treatment for 6 weeks with randomly assigned, double-blind risperidone, valproic acid, or placebo. Risperidone was flexibly dosed (mean dosage, 0.5 mg/day; range, 0.5–0.75 mg/day). The valproic acid dose was adjusted to target blood levels of 80–100 mcg/mL (mean dosage, 300 mg/day). A total of 18 patients received risperidone, 21 valproic acid, and 7 placebo. Response was defined as a ≥50% decrease in Young Mania Rating Scale (YMRS) total score or a Clinical Global Impression–Improvement (CGI-I)* rating of 1 or 2.

Results: Mean baseline YMRS scores were 30 in the valproic acid group, 32 in the risperidone group, and 31 in the placebo group. After 6 weeks of treatment, risperidone was associated with a significant decrease from baseline in mean YMRS score (-19 points; p=0.001), while the other treatments were not (valproic acid, -10 points; placebo, -4 points). Risperidone was significantly superior to both placebo (p=0.008) and to valproic acid (p=0.004) with regard to the final YMRS score, while valproic acid did not differ from placebo. Effect sizes* were 3.58 for risperidone, 1.66 for valproic acid, and 0.56 for placebo. Final CGI-I ratings indicated treatment response in 88% of the risperidone group (p=0.003) and 50% of the valproic acid group (p=0.008), and no placebo patients. The hazard ratios* for a ≥50% decline in YMRS score, relative to placebo, were 6.97 for risperidone and 1.95 for valproic acid. Risperidone-treated patients demonstrated clinical response by weeks 2–3, while valproic acid response was not evident until weeks 4–5.

One child discontinued valproic acid because of nausea, and 2 others because of anger outbursts. No patient discontinued risperidone or placebo because of an adverse event associated with

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study medication. Both active medications were associated with weight gain and increased body mass index. Treatment with valproic acid was associated with decreases in the total red blood cell count, hemoglobin, and hematocrit, while risperidone was associated with increased prolactin levels and adverse changes in liver function and cholesterol. None of the laboratory changes were clinically significant, but the time span of the study was brief.

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

Kowatch R, Scheffer R, Monroe E, Delgado S, et al: Placebo-controlled trial of valproic acid versus risperidone in children 3–7 years of age with bipolar I disorder. *Journal of Child and Adolescent Psychopharmacology* 2015;4 (May):306–313. From the Ohio State University Wexner Medical Center/Nationwide Children's Hospital, Columbus; and other institutions. **Funded by the Stanley Medical Research Foundation. The study authors declared no financial relationships with pharmaceutical sources.**

Drug Trade Names*: risperidone—*Risperdal*; valproic acid—*Depakene*, *Depakote

***See Reference Guide.**

Mortality in ADHD

According to results of a longitudinal cohort study, mortality is increased more than 2-fold in children, adolescents, and adults with ADHD. The increase observed in this study was driven largely by deaths from unnatural causes, with accidents the most common cause.

Methods: The study cohort included nearly 2 million children who were born in Denmark between 1981 and 2011. Data on ADHD and other comorbid diagnoses of interest were obtained from national registry records and from patient contacts with departments of psychiatry, pediatrics, and neurology through 2013; data from outpatient visits were only available for primarily the latter half of the study period. The main outcome was all-cause mortality after the age of 1 year. Maximum age at end of follow-up was 32 years. Unnatural causes of death (i.e., homicide, suicide, accident, or undetermined) were a secondary outcome.

Results: More than 32,000 members of the birth cohort received a diagnosis of ADHD during follow-up. Mean age at diagnosis was 12 years. Among persons with ADHD, 17% had a comorbid diagnosis of oppositional defiant disorder or conduct disorder, and 12% had a substance use disorder.

During follow-up, 107 persons with ADHD died. The mortality rate in ADHD was 5.85 per 10,000 person-years, compared with 2.21 in persons without ADHD, for an adjusted mortality ratio* of 2.07 ($p<0.0001$). Excess mortality in those with ADHD was greatest in patients who received their diagnosis after the age of 17 years (fully adjusted mortality rate ratio, 4.25; $p<0.0001$). Excess mortality related to ADHD was also greater in women and girls than in men and boys, although the difference was not statistically significant. Comorbid disorders significantly increased mortality. Compared with cohort members with no ADHD, adjusted mortality ratios were 1.5 for those with ADHD alone, 2.17 for those with ADHD plus oppositional defiant disorder/conduct disorder, 5.63 for those with ADHD plus substance use disorder, and 8.29 for those with all 3 comorbid conditions.

Of the 79 patients with ADHD for whom information on the cause of death was available, the cause was unnatural in 54 (68%); 42 of the deaths were the result of an accident. Rates of death from both natural and unnatural causes were elevated in persons with ADHD.

Discussion: This appears to be the first large-scale, long-term study of mortality in ADHD. Earlier studies have shown that ADHD is associated with greater risk of serious traffic accidents, substance use disorder, criminality, and more severe mental disorders that can affect life expectancy. Certain comorbid conditions increased mortality in the present study population but did not fully explain it.

The observation that girls and women with ADHD had greater mortality than boys and men suggests that the diagnostic threshold may be higher in females, resulting in a population with more severe and impairing symptoms, or that they may be less likely to receive treatment. The study results emphasize the importance of early identification of ADHD, especially in girls, and of treatment of comorbid oppositional defiant, conduct, and substance use disorders.

Dalsgaard S, Ostergaard S, Leckman J, Mortensen P, et al: Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. *Lancet* 2015;385 (May):2190–2196. From Aarhus University, Denmark; and other institutions. **Funded by the Lundbeck Foundation. The study authors declared no competing interests.**

***See Reference Guide.**

Timing of SSRI Response

In children and adolescents, the bulk of the antidepressant response to SSRI therapy occurs within the first 2–4 weeks of treatment, according to a meta-analysis. This study, the first meta-analysis to analyze treatment effects on a week-to-week basis, suggests there may be little benefit of prolonged treatment trials as is currently recommended.

Methods: A literature search identified published, randomized, placebo-controlled trials of SSRIs for short-term treatment of pediatric unipolar depression. Included trials provided weekly data points and used a validated symptom scale as the primary efficacy measure. The meta-analysis included 13 trials with a total of 3004 child and adolescent patients. There were 5 trials of fluoxetine, 3 of paroxetine, 1 of sertraline, and 2 trials each of citalopram and escitalopram.

Results: A statistically significant benefit of SSRI therapy relative to placebo was evident as early as 2 weeks after the start of treatment. By treatment week 2, 69% of all improvement had already occurred, and nearly all of the additional benefit was evident by week 4. No significant treatment effect of maximum SSRI dose was found. There were no differences among individual SSRIs, and no differences related to patient age or between children and adolescents. Trials published in later years were associated with a smaller treatment effect relative to placebo than earlier trials. Industry funding had no effect on results. Compared with the published literature in adults, children and adolescents experienced a smaller treatment benefit from SSRI therapy ($p<0.0001$), even when controlling for drug dosage.

Discussion: These data suggest the currently recommended 2-month treatment trials of SSRI therapy in pediatric depression may be unnecessary if treatment outcome can be predicted by response at week 2 or 4. There also appears to be no benefit of increasing doses within the therapeutic range of an SSRI. The weaker response to SSRIs in children than in adults may reflect truly lower efficacy in younger patients or it could be explained by potential attributes of pediatric trials, such as reduced sensitivity in measuring decreasing symptoms of depression.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis. However, individual study quality does not appear to have been assessed.

Varigonda A, Jakubovski E, Taylor M, Freemantle N, et al: Systematic review and meta-analysis: early treatment responses of selective serotonin reuptake inhibitors in pediatric major depressive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2015;54 (July):557–564. From the University of Vermont Medical Center, Burlington; and other institutions. **Funded by the NIH; and other sources. No study author disclosed a financial relationship with a pharmaceutical-industry source.**

Drug Trade Names*: citalopram—*Celexa*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; paroxetine—*Paxil*; sertraline—*Zoloft

***See Reference Guide.**

Trends in Adolescent Self-Injury

The number of emergency department (ED) visits for self-injuries in adolescents increased between 2009 and 2012, according to an analysis of national trauma data. The analysis identified specific subgroups of adolescents that may benefit from increased prevention efforts, including those with public insurance or no insurance and those with comorbid conditions.

Methods: Investigators analyzed records of the National Trauma Data Bank, which collects data from >700 U.S. hospitals, including nearly all Level I and Level II trauma centers. The study data spanned from 2009 to 2012 and included patients aged 10–18 years. Change over time in rates and methods of self-injury as well as potential risk factors were evaluated. However, data limitations did not allow for determination of whether the injuries were inflicted with suicidal intent.

Results: Of nearly 287,000 ED visits for trauma in adolescents, 3664 (1.3%) were for self-injury. Patients with a self-injury were more severely injured and had higher rates of multiple comorbid conditions. However, <5% of patients with self-injury had a psychiatric diagnosis. The proportion of visits for self-injury increased from 1.1% in 2009 to 1.6% in 2012 ($p<0.001$). Cutting/piercing was the most common mechanism of self-injury. There was a significant decrease in firearm injuries as a fraction of the total, from 27% to 22% ($p=0.02$). The risk of self-injury, relative to other causes, was increased in girls; older adolescents (≥15 years); those with comorbid conditions; those with public insurance or no insurance; and those with alcoholism or obesity. Adolescents most likely to die of their injuries were male, older, white, and lacking insurance coverage.

Discussion: Most children and adolescents treated in the ED for self-injury do not die; however, they are at very high risk for a subsequent successful suicide attempt, with the greatest period of risk occurring immediately after that episode. Since 2009, few studies have examined the epidemiology of adolescent self-injury. New trends include the decrease in self-inflicted firearm injuries, possibly the result of strategies to reduce access to firearms, and the apparent shift to cutting and piercing. The low number of patients with a diagnosed mental illness was a surprising finding that may reflect missed opportunities to document mental health problems and link patients to care.

Cutler G, Flood A, Dreyfus J, Ortega H, et al: Emergency department visits for self-inflicted injuries in adolescents. *Pediatrics* 2015;136 (July):28–34. From Children's Hospitals and Clinics of Minnesota, Minneapolis. **This study was conducted without funding. The authors declared no competing interests.**

Prenatal SRI Exposure and Childhood Behavior

In a longitudinal study, children exposed to serotonin reuptake inhibitor antidepressants in utero had increased internalizing behaviors and anxiety at school entry age.

Background: During development, serotonin plays a key role in neuronal proliferation, differentiation, migration, and synaptogenesis. Although SRIs are known to cross the placenta and there is substantial experimental evidence of adverse developmental effects in animals, there have been few studies to research the effects of prenatal SRI exposure on childhood outcomes.

Methods: Study participants were 110 mother-child pairs, recruited during the second trimester of pregnancy, for whom complete follow-up data were available on child behavioral outcomes at the ages of 3 and 6 years. In 44 of the pregnancies, the mother took an SRI from the time of conception and typically for all or most of the pregnancy. Child outcomes

were assessed by the mother using the Child Behavior Checklist (CBCL) at age 3 years and the MacArthur Health and Behavior Questionnaire (HBQ-P) when the child was 6 years old. Maternal anxiety and depression were also assessed throughout pregnancy and follow-up.

Results: Children exposed to SRIs prenatally were more likely than those who were not exposed to be born preterm (14% vs. 3%; p=0.036), and they were born at an earlier gestational age (39 vs. 40 weeks; p=0.001). These children were also smaller than average and had lower Apgar scores.

Exposed children had higher levels of internalizing behaviors and anxious/depressed symptoms at ages 3 years and 6 years than unexposed children. They were more likely to meet clinical thresholds for internalizing behaviors at age 3 (16% vs. 1.5%; p=0.004) and at age 6 (14% vs. 3%; p=0.036). The 2 groups did not differ with regard to externalizing behavior or attention.

Current maternal depression when the child was aged 3 or 6 years was also significantly associated with increased internalizing, externalizing, and anxious behavior at those ages. However, in a multivariate model, in-utero SRI exposure remained associated with internalizing and anxious behavior scores after controlling for current maternal depression, depression during pregnancy, and multiple other risk factors.

Discussion: Results of this study suggest that developmental exposure to maternal depression or anxiety and to the medications used to treat maternal mood disturbances are associated with increased levels of internalizing behaviors and anxiety at school age. However, several limitations of the study should be noted. The relationship between the timing and duration of the SRI exposure and childhood behavioral outcomes could not be examined as the majority of mothers received SRIs through most of their pregnancy. In addition, given that the behavioral outcomes were based on maternal report, the possibility that the relationship between in-utero SRI exposure and childhood behavior is a result of maternal depression cannot be ruled out. Finally, maternal genetics were not evaluated and it is possible that exposed infants were genetically predisposed toward internalizing behaviors and anxiety.

Hanley G, Brain U, Oberlander T: Prenatal exposure to serotonin reuptake inhibitor antidepressants and childhood behaviors. *Pediatric Research* doi 10.1038/pr.2015.77. From the University of British Columbia (UBC), Vancouver, Canada. **Funded by the Child and Family Research Institute (UBC); and the Canadian Institutes of Health Research. The authors declared no conflicts of interest.**

Transdermal Methylphenidate Skin Changes

According to a warning issued by the FDA, permanent loss of skin color can occur with use of the methylphenidate transdermal system (*Daytrana*).

The skin condition, known as chemical leukoderma, is not physically harmful but is disfiguring. In addition, the condition is not reversible, which can cause patients' emotional distress. The lightened skin sites associated with the methylphenidate patch were reportedly as large as 8 inches in diameter. *Daytrana* labeling has been updated to reflect the risk.

Patients and caregivers should monitor users for new areas of lightened skin, particularly under where the patch has been applied, and alternate treatments should be considered for patients who experience skin color changes.

Daytrana Patch (methylphenidate transdermal system): Drug safety communication—Permanent Skin Color Changes. Available at www.fda.gov/safety/medwatch.

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.

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.

Mortality Ratio: A quantity, expressed as either a ratio or percentage, quantifying the increase or decrease in mortality of a study cohort with respect to the general population.

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 are posted at www.alertpubs.com.

CHILD & ADOLESCENT
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Dystonia After Stimulant Discontinuation

Use of combined stimulants and atypical antipsychotics is common in patients with ADHD and comorbid anxiety, tics, or aggression, and the combinations appear to be safe. Because of their short acting nature, it is believed that stimulant medications can be discontinued at will (e.g., for weekends, drug holidays) without adverse effects. However, several recently reported cases suggest that this may not be the case for patients receiving treatment with concomitant aripiprazole.

A 9-year-old girl with ADHD had been taking 50 mg/day methylphenidate CD with a 5-mg methylphenidate booster dose after school. After receiving a comorbid diagnosis of reactive attachment disorder, she was started on 1 mg aripiprazole b.i.d. and demonstrated behavioral improvement. However, she presented 10 days later with a dystonic reaction—severe muscle contraction of the jaw. Aripiprazole doses were held, and she received up to 25 mg/day diphenhydramine for 2 days. The dystonia resolved. Her guardian reported that she had stopped administering the methylphenidate when she noticed improvement with the aripiprazole.

A 7-year-old boy with ADHD had initially experienced improvement with up to 30 mg/day amphetamine salts. He presented with aggressive episodes and sporadic facial tics, and 2 mg/day aripiprazole was added. Over the subsequent 2 weeks, the patient demonstrated significant improvement in behavior. The parents then neglected to give the child the stimulant for several days, and he experienced 3 episodes of neck spasms in 1 day, followed by a clearer dystonic neck contraction the next day. After aripiprazole was reduced to 1 mg/day and dextroamphetamine was restarted, the dystonic reaction resolved.

Discussion: Stimulants inhibit dopamine reuptake, which increases levels of synaptic dopamine. Aripiprazole has a high affinity for the striatal D2 dopamine receptors. When dopamine is elevated in the synaptic cleft, aripiprazole acts as an antagonist, but when dopamine is low in the synaptic cleft, it likely acts as a partial dopamine agonist. Dopamine levels are usually

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high when aripiprazole is added to a stimulant, thus reducing postsynaptic dopamine effects. Abruptly stopping the stimulant could cause a natural drop in dopamine that would be replaced by the less potent aripiprazole, thus possibly causing dystonia.

Parraga H, Sherman B: Acute dystonia after stimulant discontinuation in 2 ADHD children receiving aripiprazole [letter]. *Journal of Clinical Psychopharmacology* 2015; 35 (August):480–481. From the Department of Child and Adolescent Psychiatry at the Fourth Street Clinic, Springfield, IL. **The authors declared no competing interests.**

Drug Trade Names*: aripiprazole—*Abilify*; methylphenidate, extended-release CD—*Metadate CD

Assessment Measure for Nonsuicidal Self-Injury

The Ottawa Self-Injury Inventory (OSI), a self-report measure of nonsuicidal self-injury (NSSI), was validated in a sample of adolescent inpatients.[1] The OSI items incorporate 4 factors that represent different functions of NSSI and a separate factor for addictive features, which may be helpful in selecting specific treatments.

Background: Many adolescents may not reveal the extent of their NSSI in an initial clinical interview out of shame or difficulty expressing themselves, and therapists' time may be too limited to explore NSSI fully. Therefore, a pencil-and-paper questionnaire may enhance detection of NSSI. However, there are currently no standardized self-report measures of NSSI for clinical use. The OSI was previously validated in a community sample of self-injuring university students,[2] and a 4-factor model of the functions of NSSI—Internal Emotion Regulation, Social Influence, External Emotion Regulation, and Sensation Seeking—was suggested. The present study was conducted to validate the OSI in a clinical sample.

Methods: Study participants were adolescents consecutively admitted to an inpatient unit that provides crisis management, assessment, and stabilization, with a mean length of stay of about 5 days. A total of 94 participants (mean age, 16 years; 81% female) with a lifetime history of NSSI completed the OSI >2 days after admission. The inventory evaluates the occurrence, frequency, level of motivation to stop, types and functions and potential addictive features of self-injury. The functions of NSSI are measured by the patient indicating the degree to which each specific item corresponds with their reasons for engaging in NSSI; scores range from 0 (never a reason) to 4 (always a reason). To assess addictive features of NSSI, 7 questions were modified from the DSM-IV-TR criteria for substance dependence to incorporate addictive features of NSSI. About half of the sample reported daily or weekly self-injury, and 73% reported co-occurring suicidal ideation and/or behavior.

Results: The 4-factor function model was confirmed in this clinical sample. Two items from the Social Influence factor (i.e., to diminish sexual arousal and to get care/attention from other people) were not significantly correlated with NSSI and were dropped from the model. Two others that reflected suicidal ideation and behaviors were found to be redundant. The validity of the Addictive Features scale were confirmed, and higher scores on the scale were correlated with more frequent NSSI (correlation coefficient [r],* 0.48; $p<0.001$). The Addictive Features factor was significantly correlated with each of the 4 function factors ($r=0.30–0.44$; $p<0.01$). Higher scores on each of the function factors except External Emotion Regulation were associated with greater frequency of NSSI. Higher Addictive Features scores were also associated with increased frequency of NSSI.

Discussion: There is some controversy over whether NSSI can become an addictive behavior. Of several available self-report measures of NSSI, only the OSI assesses potential addictive features of the behavior. The OSI can also provide information on the functions of NSSI that may help with selection among evidence-based treatments. Young people with high scores on the Internal Emotional Regulation function might benefit from assessment of mood and anxiety disorders and from dialectical behavior therapy or cognitive behavioral therapy.

High Social Influence functions may indicate a good fit with Mentalization-based therapy. Significant addictive features may suggest a harm reduction approach with motivational interviewing. The OSI can be downloaded free of charge for public institutions and for research purposes at www.insync-group.ca/publications/OSI_clinical_October_20051.pdf

[1]Nixon M, Levesque C, Preyde M, Vanderkooy J, et al: The Ottawa Self-Injury Inventory: Evaluation of an assessment measure of nonsuicidal self-injury in an inpatient sample of adolescents. *Child and Adolescent Psychiatry and Mental Health* 2015; doi 10.1186/s13034-015-0056-5. From Queen Alexandra Centre for Children's Health, Victoria, Canada; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

[2]Martin J, et al: Psychometric properties of the functions and addictive features scales of the Ottawa Self-Injury Inventory: a preliminary investigation using a university aged sample. *Psychological Assessment* 2013; doi 10.1037/a0032575.

***See Reference Guide.**

DBT for Self-Injurious Adolescents

In an open-label, naturalistic treatment trial, adolescents with borderline personality disorder and self-injurious thoughts and behaviors experienced significant reductions in suicidal ideation and self-harm with an adapted form of dialectical behavioral therapy for adolescents (DBT-A).

Methods: Study participants were referred to an outpatient clinic at a dedicated, university-based psychiatric hospital. Patients were offered a 15-week course of DBT-A if they had features of borderline personality disorder with self-injurious thoughts and behaviors, met minimum severity criteria on the Suicidal Ideation Questionnaire (SIQ), and demonstrated adequate motivation for the program. DBT-A consisted of 15 weekly group sessions and 14 weekly individual sessions. To accommodate resource limitations, the program was modified from its initial form to provide less parent involvement (parents attended 4 group sessions rather than weekly multi-family skills training) and telephone consultation during regular office hours, rather than around the clock. The primary efficacy outcome was change from baseline on the SIQ.

Results: Of 90 adolescents who met inclusion criteria, 61 (57 girls) agreed to participate and 23 completed treatment. Follow-up data were available for 20 completers and 11 non-completers. Of multiple factors investigated as possible predictors of attrition, only 2—impulsivity and problematic drug use—were significantly associated with noncompletion.

Among all participants with follow-up data, the median SIQ score decreased from 131 at baseline to 77 at post-treatment ($p<0.001$; effect size,* 0.89). Final scores did not differ between completers and non-completers, perhaps because of the small sample size.

Self-harm was measured using chart review throughout treatment and during the 4 months following treatment completion in 42 patients. In the 4 months before treatment, 86% of patients were engaging in self-harm. During the 4 months of treatment, this was reduced to 55%, and then further reduced to 38% at the 4-month follow-up.

Discussion: There are several indications that the present study population was more severely ill than those previously described in clinical trials of DBT, including higher baseline SIQ scores and a higher rate of substance-use disorders. It should be noted that, despite improvement, post-treatment SIQ scores for suicidal ideas remained above the population 90th percentile in the majority of participants. Without a control group for comparison, alternative explanations for the study results are possible. However, the lack of any new onset persistent self-harm from pre- to post-treatment or completed suicides supports the safety of outpatient DBT-A in a structured group setting for this patient population, and additional study appears to be warranted.

Courtney D, Flament M: Adapted dialectical behavior therapy for adolescents with self-injurious thoughts and behaviors. *Journal of Nervous and Mental Disease* 2015;203 (July):537–544. From the University of Toronto; and the University of Ottawa, Canada. **Funded by the Royal Ottawa Mental Health Center. The authors declared no competing interests.**

***See Reference Guide.**

Gluten-Associated Psychosis

A 14-year-old girl had a 2-year history of recurrent gastrointestinal (GI) complaints and intermittent psychiatric symptoms including irritability, crying spells, apathy, and eventually psychotic symptoms.[1] Over the course of her treatment, she had received a benzodiazepine for suspected conversion somatic disorder. However, psychiatric symptoms worsened and she began to experience complex hallucinations. Laboratory study results were unremarkable with the exception of abnormal autoimmune parameters. These abnormalities in combination with worsened psychotic symptoms suggested autoimmune encephalitis, and steroid treatment was started. She experienced partial improvement but continued to experience emotional apathy, poverty of speech, social withdrawal, and self-neglect. Several months later, she was referred to a psychiatric unit with suspected relapse of autoimmune encephalitis manifest with relevant confusion, ataxia, severe anxiety, and paranoid delusions. Steroid treatment was restarted along with immunoglobulins, but she was readmitted several times in subsequent months with psychotic symptoms.

Two years after her initial presentation, intermittent psychotic symptoms persisted and suicidal ideation developed; olanzapine (*Zyprexa*) was initiated. Because GI complaints were also present and she had experienced substantial weight loss, a nutritionist recommended a gluten-free diet. Within 1 week of removing gluten from her diet, both the GI and psychiatric symptoms improved dramatically. Occasional inadvertent gluten exposure produced recurrence of psychotic symptoms within hours that resolved over 2–3 days. To confirm the episodes were gluten-associated, she underwent a wheat-flour challenge and hallucinations recurred. Olanzapine was stopped, and she remained psychiatric-symptom free over 9 months of follow-up with the gluten-free diet.

The pathogenesis of gluten-associated neuropsychiatric symptoms is unknown. It is possible that increased intestinal permeability may allow gluten peptides to cross the intestinal membrane and the blood brain barrier, affecting the endogenous opiate system and neurotransmission or that gluten peptides initiate an immune response in the brain. While this appears to be the first report of gluten-associated psychosis in a pediatric patient, it has been described in at least 1 adult patient as well.[2]

[1]Lionetti E, Leonardi S, Franzonello C, Mancardi M, et al: Gluten psychosis: confirmation of a new clinical entity. *Nutrients* 2015;7:5532–5539. From the University of Catania, Italy; and other institutions. **The study authors declared no financial relationships with pharmaceutical-industry sources.**

[2]Genuis S, Lobo R: Gluten sensitivity presenting as a neuropsychiatric disorder. *Gastroenterology Research and Practice* 2014; doi 10.1155/2014/293206. From the University of Alberta, Edmonton, Canada.

Stimulants in Long-QT Syndrome

According to results of a retrospective study, ADHD medications are associated with a 3-fold increase in risk of cardiac events in patients with long-QT syndrome (LQTS). Risk appears to be particularly high in male patients.

Background: LQTS is a hereditary disorder characterized by a prolonged corrected QT (QTc) interval of >450 ms in males and >470 in females. Patients with LQTS have a predisposition to cardiac events including syncope, aborted cardiac arrest, and sudden cardiac death. Sympathetic blockade, usually with a beta-blocker, is the major goal of LQTS therapy. ADHD medications can interfere with this sympathetic blockade, putting patients at greater cardiac risk.

Methods: Data from an LQTS registry that included 48 patients taking any type of ADHD medication were retrospectively analyzed. Each patient was matched for age, gender, and baseline QTc duration with 2 controls with LQTS who had never been exposed to ADHD

medication. Patients were followed at yearly intervals for the primary study endpoint of first occurrence of a cardiac event, defined as syncope, aborted cardiac arrest, or LQTS-related sudden cardiac death.

Results: At enrollment, participants were an average age of 11–13 years; 38% were female. The mean baseline QTc interval was 471 ms. About one-third of patients were receiving beta-blocker therapy for LQTS. A similar proportion of both groups, about 25%, had a history of cardiac events, almost exclusively syncope, before the study baseline. The average follow-up time was 7–8 years. A total of 44 patients received treatment with stimulants only, 4 with non-stimulants, and 4 with a combination.

A total of 17 patients taking ADHD medication experienced ≥1 cardiac event during follow-up, compared with 15 comparison subjects (35% vs. 16%; p=0.007). Syncope accounted for nearly all of these events. There was 1 sudden cardiac death in each group. Of 3 patients who had an aborted cardiac arrest, 2 were taking ADHD medication. At 5 years of follow-up, the average heart rate was 11 bpm higher in patients taking ADHD medications than in controls. Average QTc duration did not differ between the groups.

The cumulative probability of cardiac events, estimated out to 15 years, was 62% in the group receiving ADHD medication and 28% in the comparison group (hazard ratio,* 3.07; p<0.03). The increased risk was confined to male patients who were taking ADHD medications, who had a greater than 6-fold risk elevation (hazard ratio, 6.8; p=0.04).

Discussion: It is possible that the increase in heart rate, leading to increased vulnerability to common arrhythmia triggers, could explain the results of this study. Regardless of the mechanism, the substantial increase in cardiac risk makes limiting the use of ADHD medications in patients with LQTS to those whose ADHD symptoms clearly require therapy, as well as using the lowest effective dose, and maintaining close follow-up.

Zhang C, Kutyifa V, Moss A, McNitt S, et al: Long-QT syndrome and therapy for attention deficit/hyperactivity disorder. *Journal of Cardiovascular Electrophysiology* doi 10.1111/jce.12739. From the University of Rochester, NY; and Case Western Reserve University, Cleveland, OH. **Funded by the NIH; and the GeneDx genetic testing company. The authors declared no competing interests.**

***See Reference Guide.**

Racemic Amphetamine

In a manufacturer-sponsored trial, racemic amphetamine sulfate (*Evekeo*), given once or twice a day, was effective and well tolerated in children with ADHD.

Background: Amphetamines have 2 isomers with different pharmacokinetics, mechanisms of action, and effect profiles. Some amphetamine products include only dextro (D)-amphetamine, while others consist of a ratio of 3:1 D-amphetamine to levo (L)-amphetamine. The racemic amphetamine investigated in this study consists of equal proportions of D- and L-amphetamine. It received FDA approval for treating ADHD in September 2014.

Methods: Study participants were children, aged 6–12 years, with a diagnosis of ADHD of any type, at least mild illness severity on the Clinical Global Impression–Severity (CGI-S) scale, and a baseline score in the 90th percentile for age and gender on the ADHD Rating Scale-IV (ADHD-RS-IV). After discontinuation of previous medications and a 2-week screening and baseline evaluation, all patients underwent an 8-week dose optimization phase with twice-daily open-label racemic amphetamine. Patients who tolerated a ≥10-mg dose of amphetamine underwent two 1-week phases of crossover treatment with the active drug or placebo, in random order. Participants were evaluated during a 4-hour laboratory classroom session at the end of each week of randomized treatment. The primary efficacy measure was the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale, administered 2 hours post-dose

during the school evaluations. A secondary efficacy outcome was the duration of action of a single morning dose. (The afternoon dose was not given during the school sessions.)

Results: During the open-label, dose-optimization phase, ADHD-RS-IV total scores improved from about 41 at baseline to 13 at the end of 8 weeks. A total of 85 patients (88%) had a ≥50% improvement in ADHD-RS-IV score (responders). At study entry, about 10% of patients were rated as severely ill on the CGI-S, 37% were markedly ill, and 50% were moderately ill. At the end of the open-label phase, 33% of patients were considered normal, 27% were borderline ill, 37% were mildly ill, 3% were moderately ill, and none were markedly or severely ill.

A total of 97 patients entered the randomized treatment phase, and 95 completed the 2 classroom evaluations. The mean SKAMP combined score on the test day was 10.3 during treatment with racemic amphetamine and 18.1 with placebo ($p<0.0001$). Subgroup analyses showed the results were similar regardless of patient age, gender, and ADHD subtype. Racemic amphetamine was statistically superior to placebo beginning 45 minutes post-dose and lasting until the final evaluation (10 hours post-dose) with the largest difference observed at 4 hours. Results for the SKAMP Attention and Deportment subscales were similar to the combined score.

Adverse events of the medication were consistent with amphetamine use. Decreased appetite was the most common adverse effect. Two patients had severe insomnia.

Discussion: D-amphetamine, which is the main component of available amphetamine preparations, has stronger nervous system excitatory effects than L-amphetamine, while the L-isomer has more potent cardiovascular effects. As such, different D- to L-isomer ratios could alter adverse effect profiles. For example, the L-isomer has been shown to cause less appetite suppression than the D-isomer. In addition, the L-isomer has a longer half-life, which may underlie the prolonged efficacy of immediate-release *Evekeo* in this study.

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

Childress A, Brams M, Cutler A, Kollins S, et al: The efficacy and safety of Evekeo, racemic amphetamine sulfate, for treatment of attention-deficit/hyperactivity disorder symptoms: a multicenter, dose-optimized, double-blind, randomized, placebo-controlled crossover laboratory classroom study. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (June):402–414. From the Center for Psychiatry and Behavioral Medicine, Las Vegas, NV; and other institutions. **Funded by Arbor Pharmaceuticals, Atlanta, GA. All study authors disclosed financial relationships with commercial sources, including Arbor Pharmaceuticals, manufacturer of Evekeo.**

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Correlation Coefficient (r): A measure of the closeness of the relationship between 2 variables. The value of r can range from -1 to 1. An r value near 1 indicates a strong positive relationship. An r-value close to zero indicates no relationship, and a negative r value indicates a negative relationship.

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 1 group has half the risk of the other 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 are posted at www.alertpubs.com.

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Clozapine Monitoring Changes

A new centralized clozapine risk evaluation and mitigation strategy (REMS) program has been created to replace the 6 individual registries previously maintained by individual manufacturers. All requirements for prescribing, dispensing, monitoring, and receiving clozapine products will now be incorporated into the single REMS program. (See www.clozapinerems.com.) Patients already receiving the medication will be automatically transferred to the new registry. The transition is scheduled to begin in October 2015.

In addition to the centralized registry, the FDA has also updated the monitoring requirements for neutropenia in patients receiving clozapine. Neutropenia will now be evaluated only by absolute neutrophil count (ANC), rather than in conjunction with white blood cell counts. This change is designed to allow patients with lower ANC to continue clozapine treatment and to allow for treatment of patients with benign ethnic neutropenia, who were not eligible to receive clozapine under the old REMS program. According to the FDA, the changes increase "prescribers' ability to make individualized treatment decisions if they determine that the risk of psychiatric illness is greater than the risk of recurrent severe neutropenia."

FDA drug safety communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines. Available at http://www.fda.gov/Drugs/DrugSafety.

Adverse Drug Effects in Very Young Children

There is very little data available on adverse effects of psychotropic medications in very young children. According to results of an observational study, compared with older children, very young children have higher liability for adverse events with some psychotropic medications.

Methods: Study participants were 158 children, aged 3–7 years (mean age, 5.5 years), who received treatment at a hospital-based day program for emotional and behavioral problems. Most children in the sample had severe problems and had failed lower levels of care. Each

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child's parents reported medication adverse effects upon admission and weekly thereafter using the 45-item Pediatric Adverse Events Rating Scale (PAERS)–Parent Version. The treating child psychiatrist also completed a clinician version of the instrument. The frequency of adverse events was compiled for 6 commonly used prescription drugs and 1 OTC agent: methylphenidate; amphetamine–dextroamphetamine mixed salts; fluoxetine; sertraline; guanfacine; clonidine; and melatonin. Atypical antipsychotics were prescribed too infrequently to be included in the analysis.

Results: No adverse events were reported for sertraline, prescribed for 14 patients, or for melatonin, used by 47 patients. Overall reported adverse effects were highly variable with the other study drugs, with few drug–side effect pairs occurring in >2 or 3 patients. The highest rate of adverse events occurred with fluoxetine; 41% of the 17 patients who received the agent reported an adverse effect, most commonly impulsivity and concentration difficulty (12% each). Compared with sertraline, the odds ratio* for experiencing an adverse effect with fluoxetine was 17. Irritability/anger and mood lability each affected 6 of the 47 children receiving methylphenidate (13%); sadness/depression or apathy affected 4 children taking methylphenidate (9%). The overall frequencies of adverse events were similar for the 2 stimulants—28% for methylphenidate and 21% for mixed amphetamine salts—with mood-related difficulties and decreased appetite the most common. Adverse event rates were also statistically similar for guanfacine and clonidine (10% and 17%, respectively), with fatigue the most commonly reported adverse effect in both. Patient age did not appear to affect the frequency of adverse effects, and it could not be determined whether dosage had any effect.

Discussion: Research on the adverse effects of psychotropic medication in young children with severe psychiatric illness lags far behind prescribing practices. Compared with the existing literature in older children and adults, rates of adverse effects of some medications (e.g., methylphenidate, fluoxetine) appear higher in young children, while the rate with sertraline appears lower. The PAERS is a comprehensive, easy-to-use measurement instrument that the study authors recommend for systematically assessing side effects in clinical practice.

Lee C, Williamson L, Martin S, DeMarco M, et al: Adverse events in very young children prescribed psychotropic medications: preliminary findings from an acute clinical sample. *Journal of Child and Adolescent Psychopharmacology* 2015;8 (August):509–513. From Brown University, Providence, RI; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

Drug Trade Names*: amphetamine–dextroamphetamine mixed salts—*Adderall*; clonidine—*Catapres, Kapvay*; fluoxetine—*Prozac*; guanfacine—*Intuniv, Tenex*; methylphenidate—*Ritalin*; sertraline—*Zoloft

***See Reference Guide.**

Functional Neuroimaging in Pediatric Depression

A meta-analysis of neuroimaging studies in young people with major depressive disorder showed a consistent pattern of functional abnormalities in several networks linked with the phenomenology of depression. These findings and the existing neuroscience literature may explain seemingly disparate symptoms of depression and may help develop targeted interventions.

Methods: The meta-analysis included published functional MRI studies that compared neural activation in young people (aged 4–24 years) with depression and healthy controls, using a voxelwise whole-brain analysis of task-based activation data. Data from all studies were merged, and patients and controls were compared for each voxel throughout the whole brain to identify abnormal findings consistent across diverse experimental conditions. Studies involving emotional processing tasks or executive functioning tasks were also analyzed separately. The studies that included emotional processing were further subdivided into those that compared positive versus neutral emotional valences and those with negative versus neutral valences.

Results: The analysis included 14 studies, with a total of 246 subjects who were experiencing a current episode of depression and 274 healthy controls. The studies comprised a broad range of tasks, conditions, and subject ages (mean age, 15 years) and special circumstances, such as first-episode and medication-naive patients.

The studies showed reliably different activation levels in several brain regions both in general and task-specific tests. Overall, young people with depression showed consistent hyperactivity in the left dorsolateral prefrontal cortex (DLPFC; $p<0.03$); left subgenual anterior cingulate cortex ($p<0.05$); right anterior insula ($p<0.005$); bilateral thalamus ($p<0.01$); left parahippocampal gyrus ($p<0.003$); and left superior temporal cortex (STC; $p<0.03$); as well as hypoactivity in the right caudate ($p<0.03$).

Executive-function processing tasks showed significant depression-related hypoactivity in the right dorsal cingulate cortex, right dorsal anterior insula, and left cuneus. With affective processing tasks, young people with depression had hyperactivity at the left DLPFC, bilateral thalamus, and left parahippocampal gyrus. In valence-related emotional processing tasks, hypoactivity of the right posterior insula was demonstrated in positive-versus-neutral tests and hyperactivity in the left DLPFC and left STC in negative-versus-neutral tests.

Aggregated and emotional processing whole brain maps were correlated with affective processing, negative valence emotions, and high arousal. Executive-function brain maps were strongly and inversely correlated with terms related to cognitive processing, attention shifting, and response inhibition.

Discussion: These observations support the growing recognition of depression as a biologically driven dimensional system involving multiple networks and their emotional or functional correlates. Some regions involved in emotional processing that are hyperactive in depression appear to be components of the default mode network, which subserves self-referential processing and is associated with maladaptive rumination. Underactivity was demonstrated in a region that normally inhibits the default mode and facilitates executive functioning and attention shifting from rumination to adaptive processing.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis; however, individual study quality does not appear to have been assessed.

Miller C, Hamilton J, Sacchet M, Gotlib I: Meta-analysis of functional neuroimaging of major depressive disorder in youth. *JAMA Psychiatry* 2015; doi 10.1001/jamapsychiatry.2015.1376. From Stanford University, CA; and the Laureate Institute for Brain Research, Tulsa, OK. **Funded by Stanford University; and other sources. The authors declared no conflicts of interest.**

***See Reference Guide.**

Childhood Maltreatment and Suicide Attempts

In a nationally representative sample, childhood maltreatment was associated with risk of a suicide attempt and with earlier age at first suicide attempt. The types of maltreatment examined acted on suicide risk through a shared mechanism, with sexual abuse showing an additional independent effect.

Methods: Data were analyzed from the National Epidemiologic Survey on Alcohol and Related Conditions, conducted by the U.S. Census Bureau. Face-to-face interviews with adults were conducted in 2 waves, in 2001–2002 and 2004–2005; data for this study were drawn from the latter wave of interviews. Participants were administered a structured questionnaire regarding the occurrence and frequency of 5 types of childhood maltreatment—emotional neglect, physical neglect, emotional abuse, physical abuse, and sexual abuse—and they were asked about the occurrence of suicide attempts, age at first attempt, and whether there was >1 attempt. The

analysis was adjusted for the presence of Axis I and Axis II disorders, among many other covariates. A structural equation model was used to assess the shared and specific effects of each type of maltreatment.

Results: Among nearly 35,000 respondents, 1265 reported having attempted suicide. After adjustment for sociodemographic characteristics and psychopathology, each type of maltreatment was associated with increased risk of a suicide attempt, with adjusted odds ratios* ranging from 4.2 for emotional neglect to 6.4 for sexual abuse. Each type of abuse was associated with a younger age at first suicide attempt, but not with risk of >1 attempt. The structural analysis showed a shared effect of all maltreatment types, with an additional independent contribution of sexual abuse.

Discussion: A shared effect of all types of maltreatment has not been previously reported. Although the mechanisms are unknown, maltreatment may disrupt developmental processes that strengthen emotional regulation and interpersonal skills, leading to insecure attachment styles, impaired emotional perceptions and reward processing, and increased impulsivity and neuroticism. Other mechanisms may be dysregulation of the hypothalamic-pituitary-adrenal stress response and long-term decreased social support. The stronger effect of sexual abuse is consistent with other studies and may be explained by its greater effect in disrupting developmental processes. The overall study results suggest that preventing all types of child maltreatment and applying interventions that target the affected developmental mechanisms could lead to substantial progress in suicide prevention.

Hoertel N, Franco S, Wall M, Oquendo M, et al: Childhood maltreatment and risk of suicide attempt: a nationally representative study. *Journal of Clinical Psychiatry* 2015;76 (July):916–923. From New York State Psychiatric Institute/Columbia University; and other institutions. **Funded by the NIH; and other sources. Two study authors disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

***See Reference Guide.**

Iron Homeostasis with Risperidone

In a group of pediatric patients, risperidone (*Risperdal*)-related weight gain was associated with a reduction in body iron reserves.[1] The clinical effects of iron depletion are unknown but could include reduced efficacy and tolerability of psychotropic medications.

Background: These authors previously reported risperidone-related iron depletion in a cross-sectional study,[2] although pretreatment iron concentration was not assessed. The present investigation was carried out to replicate those results longitudinally and to examine the effects of risperidone discontinuation and weight loss.

Methods: Two study populations were included in the present analysis. Longitudinal assessment of body weight and ferritin was carried out as part of a clinical trial of risperidone, alone or with behavioral therapy, in children, aged 4–13 years, with autism spectrum disorder and disruptive behavior. In addition, follow-up assessment was carried out in participants in the original cross-sectional study who received treatment with risperidone for any indication. Patients were excluded from the analysis if they had a >75% increase in ferritin level or elevated C-reactive protein, indicative of acute inflammation.

Results: A total of 73 patients were evaluated as part of the clinical trial. By follow-up (mean, 18 weeks), patients had an average increase of nearly 1 point in age- and gender-adjusted body mass index (BMI) and a 15% reduction in ferritin concentration. There was a significant inverse association of change in the 2 outcomes ($p<0.003$); every 1-point increase in BMI was associated with an 18% reduction in ferritin. Red blood cell count and hemoglobin levels did not change during the study.

Patients from the cross-sectional study (n=96) were available for follow-up 18 months after enrollment and included 70 who continued taking risperidone, 11 who switched to another antipsychotic, and 15 who were no longer receiving any antipsychotic. Adjusted BMI increased in patients who switched to another antipsychotic and decreased in those who stopped all antipsychotics. In the latter group, reduction in BMI was associated with higher ferritin concentrations at follow-up (p=0.01). Patients who lost weight but continued taking risperidone did not show improved iron status.

Discussion: These results suggest that clinicians should monitor iron status in patients receiving long-term risperidone treatment. In children, iron deficiency has been associated with cognitive impairment. In the initial cross-sectional study, iron concentrations were inversely associated with prolactin concentrations, presumably secondary to a reduction in dopamine D2 receptor density in the anterior pituitary, induced by iron depletion. Further research is needed to determine whether other antipsychotics adversely affect iron status and whether iron supplementation would be indicated in patients with low iron reserves.

[1]Calarge C, Ziegler E, Del Castillo N, Aman M, et al: Iron homeostasis during risperidone treatment in children and adolescents. *Journal of Clinical Psychiatry* 2015; doi 10.4088/JCP.14m09258. From the University of Iowa, Iowa City; and other institutions. **Funded by the National Alliance for Research on Schizophrenia and Depression; and the NIH. Four study authors declared financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

[2]Calarge C, et al: Iron deficiency in pediatric patients in long-term risperidone treatment. *Journal of Child and Adolescent Psychopharmacology* 2013;23:101–109.

Young-Adult Outcomes of Childhood Psychiatric Problems

According to results of a longitudinal study, common childhood psychiatric problems predict adverse health, legal, financial, and social outcomes in early adulthood. The effects observed in this study persisted even when the psychiatric problems were no longer present in adulthood and when patients did not meet full diagnostic criteria for a disorder.[1]

Methods: The Great Smoky Mountains Study is a longitudinal study of a sample of children living in predominantly rural counties in North Carolina. A total of 1420 children were first interviewed at ages 9, 11, or 13 years and then followed with annual assessments until age 16 years, with additional interviews at 19, 21, and 25 years. The study period spanned 1993 to 2010. Childhood impairment in 17 areas of functioning was assessed using the Child and Adolescent Psychiatric Assessment. The criterion for symptomatic impairment was met when children showed impairment from psychiatric symptoms that did not meet the full DSM-IV criteria for any disorder. A total of 12 different adult outcomes were assessed in 4 categories—i.e., health, legal, financial, and social. The outcomes included multiple addictions, suicidality, incarceration, early parenthood, and multiple divorces. Analyses were adjusted for multiple adverse experiences in childhood and for adult psychiatric disorders and subthreshold impairment.

Results: Of the total sample, 26% met criteria for a common behavioral or emotional disorder at some point between the ages of 9 and 16 years, 31% had subthreshold psychiatric problems, and 43% were free of impairment. Follow-up data in young adulthood were available for about 90% of the original sample. For virtually all of the adverse outcomes, risks were higher in cases than noncases, higher in impaired young people than noncases, and often higher in cases than those with subthreshold impairment only. A total of 60% of children with a diagnosed disorder had an adverse outcome as a young adult, compared with 42% of children with subthreshold symptoms and 20% of noncases. Psychiatric and subthreshold cases accounted for nearly 80% of individuals with an adult problem. Cases had significantly greater risk of a poor outcome than noncases (odds ratio,* 5.9; p<0.001), as did those with subsyndromal impairment

(odds ratio, 2.9; p<0.001). Risks were attenuated but remained significant after adjustment for other factors including adult psychiatric problems and adult subthreshold problems.

An important aim of the study was to examine the specificity* of association between child and adult problems. Two diagnoses—depression and conduct disorder—were associated with elevated risk of an adverse outcome in adjusted models. (See table.)

Odds ratios for adverse young adult outcomes by childhood diagnosis		
	Any 1 adverse outcome	≥2 adverse outcomes
Childhood Diagnosis	Odds Ratio	Odds Ratio
Depression	2.6†	1.5
Anxiety	0.7	1.0
ADHD	1.7	1.7
Conduct disorder	2.8†	2.9†
Oppositional defiant disorder	1.2	0.6
Substance use disorder	2.0	1.8

†p<0.05
All comparisons adjusted for gender, family socioeconomic status, childhood maltreatment, and adult psychiatric disorders.

Editorial: The clinical implications of a link between childhood and adult psychopathology are not clear, and these study results do not explain the mechanism of the association.[2] It is possible that child and adult psychopathology have different causes but that mental health problems in childhood may increase risk of adult problems by such indirect mechanisms as alienating peers and family, limiting educational opportunities, and increasing risks of incarceration or brain injuries. Alternatively, some or all of the genetic and environmental causes of lifetime psychopathology operate early in life. A third explanation suggests that common adverse influences operate throughout life. The 3 hypotheses, which are not mutually exclusive, have different implications for the best age and method for intervention.

[1]Copeland W, Wolke D, Shanahan L, Costello J: Adult functional outcomes of common childhood psychiatric problems: a prospective, longitudinal study. *JAMA Psychiatry* 2015;72 (September):892–899. From Duke University Medical Center, Durham, NC; and other institutions. **Funded by the NIMH; and other sources. The authors declared no competing interests.**

[2]Lahey B: Why are children who exhibit psychopathology at high risk for psychopathology and dysfunction in adulthood? [Editorial]. *JAMA Psychiatry* 2015;72 (September):865–866. From the University of Chicago, IL. **The author declared no competing interests.**

***See Reference Guide.**

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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.

Specificity: A statistical measure of the performance of binary classification tests that measures the proportion of negatives that are correctly identified (i.e., the percentage of healthy people who are correctly identified as not having the condition).

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 are posted at www.alertpubs.com.

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Amphetamine Oral Suspension

The FDA has approved the first extended-release oral amphetamine suspension (*Dyanavel XR*) for use in children aged ≥6 years.[1] The agent, developed using a patented LiquiXR™ technology, comprises both immediate- and extended-release amphetamine. The approval was based on a phase III, randomized, placebo-controlled, laboratory classroom study in 108 children, aged 6–12 years, with ADHD. The study included a 5-week, open-label, dose optimization phase, followed by a 1-week, double-blind treatment period. Participants demonstrated improvements in Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scores beginning 1 hour post dose and continuing through 13 hours. Nose bleed, allergic rhinitis, and upper abdominal pain were the most common adverse effects of treatment.

Dyanavel XR joins methylphenidate extended-release oral solution (*Quillivant XR*),[2] approved in 2012, as the only available liquid stimulant preparations.

[1]Tris Pharma receives FDA approval of Dyanavel XR (amphetamine) CII as once-daily liquid for treatment of ADHD in children [press release]. Monmouth Junction, NJ: Tris Pharma, Inc.; October 20, 2015.

[2]NextWave Pharmaceuticals receives FDA approval of Quillivant XR for once daily treatment of ADHD [press release]. Cupertino, CA: PRNewswire; October 1, 2012. See *Child & Adolescent Psychiatry Alerts* 2012;14 (November–December):66.

Brief CBT for Adolescent ADHD

A randomized trial found 2 relatively brief cognitive behavioral therapies improved ADHD symptoms, planning skills, and executive function in adolescents. Incorporating a specific focus on planning resulted in little additional benefit compared with solution-focused treatment that included no skills training.

Background: Executive-function deficits are common in adolescents with ADHD and often affect school and social functioning. While pharmacotherapy reduces core symptoms of ADHD, it does not generally affect executive function. CBT, aimed at these particular deficits, may be helpful, but most available programs are highly intensive, often consisting

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of 14–17 sessions or 5 months of twice-weekly sessions. The present study was undertaken to evaluate the efficacy of 2 shorter-term CBT interventions.

Methods: Study participants, aged 12–17 years, were recruited from 16 mental-health facilities in the Netherlands. For study inclusion, patients were required to have a confirmed ADHD diagnosis and to be enrolled in secondary school. Those who received any nonpharmacological treatment, including tutoring and remedial education, were excluded. Treatment consisted of 8 individual adolescent and 2 parent sessions, lasting 45–60 minutes each. Both treatments used motivational interviewing techniques, such as self-identified goals and collaborative treatment, to maximize autonomy and reduce attrition. The Plan My Life (PML) CBT taught a specific planning skill in each session (e.g., how to use to-do lists, prioritizing, dividing big problems into small steps, and concentration). The comparison treatment, named Solution-Focused Treatment (SFT) to make it appear as "credible" as PML, allowed the adolescent to choose a problem in each session and then receive guidance toward a solution, but it did not teach any planning skills. All participating therapists provided both treatments. The primary outcomes were parent-rated ADHD symptoms, planning skills, and executive function, measured using a combination of the Disruptive Behavior Disorders Rating Scale and the Behavior Rating Inventory of Executive Function.

Results: A total of 159 adolescents were randomly assigned to either PML (n=83) or SFT (n=76). They were representative of the ADHD population with regard to gender (74% boys), ADHD subtype (70% inattentive), and psychotropic medication use (78%). Only 4 patients in each group did not complete treatment.

Patients in both treatment groups showed considerable improvement from pretreatment to the follow-up assessment, conducted 3 months after completion of CBT. Treatment produced large, statistically significant effects on ADHD symptoms, executive function, and planning skills as well as comorbid anxiety and internalizing symptoms, with little difference in outcomes between the 2 treatments. There was a statistically nonsignificant trend toward larger improvement with PML in parent-rated executive function and planning. However, function was normal according to the Impairment Rating Scale, parent version, at follow-up in only 15% of the total sample of adolescents, compared with 6% at baseline.

Therapists reported they felt PML was better suited for adolescents with ADHD than SFT; parents also gave PML a more positive rating. Adolescents had no strong preference.

Discussion: The present study indicates relatively brief CBT may be beneficial and feasible in European and U.S. contexts. Arguably, the high proportion of participants who did not achieve normal function suggests more intensive treatment may be needed.

Boyer B, Geurts H, Prins P, Van der Oord S: Two novel CBTs for adolescents with ADHD: the value of planning skills. *European Child and Adolescent Psychiatry* 2015;24 (September):1075–1090. From the University of Amsterdam, the Netherlands. **Funded by ZonMw, the Netherlands Organization for Health Research and Development. Two authors disclosed potential conflicts of interest; the remaining 2 authors declared no conflicts of interest.**

Pediatric Mood Disorders and Atherosclerosis

Major depressive disorder and bipolar disorder confer moderately increased risk of accelerated atherosclerosis and early cardiovascular disease in children and adolescents, according to a Scientific Statement from the American Heart Association (AHA). Because pediatric mood disorders are highly prevalent and generally treatable, efforts to improve identification, monitoring, and treatment could result in substantial cardiovascular benefits.

Scientific evidence supports the addition of mood disorders to the short list of conditions that confer at least a moderate increase in cardiovascular risk (AHA "tier II" risk) in young patients.

The others, far less prevalent, are Kawasaki disease, chronic inflammatory disease, HIV, and nephrotic syndrome. These conditions are all associated with evidence of accelerated atherosclerosis before the age of 30 years. Studies that support the increased cardiovascular risk associated with pediatric mood disorders are few but convincing. Results of epidemiologic studies show increased risk of premature cardiovascular mortality and ischemic heart disease. Markers of elevated risk in young people with mood disorders include premature vascular aging (indicated by increased carotid intima-media thickness) and various indices of endothelial dysfunction.

The traditional cardiovascular risk factors of obesity, insulin resistance, and dyslipidemia have increased prevalence in young people with mood disorders. They also have disproportionate exposure to behavioral and environmental factors contributing to risk, including early mistreatment; sleep disturbance; poor nutrition; sedentary lifestyle; smoking; and alcohol and illicit-substance use. Second-generation antipsychotics, and to a lesser extent antidepressants and mood stabilizing drugs, are associated with weight gain and other adverse metabolic changes. However, direct evidence linking these drugs with cardiovascular disease is lacking, and risk has been shown to be elevated even in young people not exposed to these medications.

Treatment guidelines for cardiovascular risk reduction specific to young people with major depressive disorder or bipolar disorder are not yet available. Current guidelines for managing mood disorders do not adequately address cardiovascular risk factors in youth with depression or the importance of metabolic monitoring, even in patients with unmedicated bipolar disorder.

Goldstein B, Carnethon M, Mathews K, McIntyre R, et al: Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a Scientific Statement from the American Heart Association. *Circulation* 2015; doi 10.1161/CIR.0000000000000229. From the American Heart Association. **Two study authors disclosed financial relationships with commercial sources; the remaining 11 authors declared no competing interests.**

Targeted Prevention of Anxiety Disorders

A brief family-based cognitive behavioral intervention reduced the onset of anxiety disorders in a group of at-risk children.

Background: Offspring of parents with anxiety are vulnerable to development of anxiety disorders themselves. Untreated anxiety in young patients can lead to adverse academic and social outcomes, yet many young people with anxiety receive no treatment. Practical preventive or early intervention programs are needed for these at-risk youths.

Methods: Participating families were recruited from the community or referred by clinicians. Families were required to have ≥1 parent with a current anxiety disorder and a child, aged 6–13 years, who did not have an anxiety disorder. The parent and child were the study subjects, but other family members were invited to participate in the therapy. The active intervention was the manualized Coping and Promoting Strength program, consisting of 8 weekly 60-minute sessions and 3 optional booster sessions. The program focused on cognitive techniques to address modifiable child and parent risk factors for anxiety disorders. A comparison group received only a pamphlet with information about anxiety disorders and their treatments, without revealing the anxiety-reduction strategies taught in the active program. The control intervention was designed to represent the type of treatment these children would receive under ordinary conditions. The primary study outcome was the onset of a child anxiety disorder over 12 months of follow-up. Anxiety in children was rated using the Anxiety Disorders Interview Schedule.

Results: A total of 70 families received the Coping and Promoting Strength program, and 66 received the pamphlets. About half of the recruited children (in both groups) had significant

subclinical anxiety symptoms; only a few children had non-anxiety disorders (i.e., ADHD and enuresis). Families in the active intervention group attended an average of 9 of the 11 available sessions. The parents with the anxiety disorders attended all sessions, and the other parents were also present in half.

Anxiety disorders in the children were assessed at the completion of treatment and after 6 and 12 months. At the post-intervention assessment, anxiety disorders were present in 5 of the control subjects, compared with none of the active-treatment subjects. Over the course of the year, anxiety disorders were present in 19 and 3 patients in the groups, respectively (odds ratio,* 8.54; p<0.001). The number needed to treat* to prevent an anxiety disorder diagnosis at 1 year was 4. At all time intervals, anxiety symptom severity was significantly lower in children who participated in the program, with effect sizes* of 0.74 posttreatment and 0.62 at 12 months. According to parent reports, use of mental health services for child anxiety was lower in the group receiving treatment, although the difference was not statistically significant (22% vs. 13%).

Discussion: Most studies of anxiety disorder prevention in children have been only modestly effective and have been conducted in schools as universal prevention efforts. No program in the U.S. has previously targeted high-risk offspring of anxious parents. The targeted program described in this study was associated with larger effect sizes than those typically associated with universal prevention programs. Exploration of several theory-driven mediators of treatment effects suggests that the program worked by reducing parental modeling of anxiety and global distress, which reduced child anxiety symptoms.

Ginsburg G, Drake K, Tein J-Y, Teetsel R, et al: Preventing onset of anxiety disorders in offspring of anxious parents: a randomized controlled trial of a family-based intervention. *American Journal of Psychiatry* 2015; doi 10.1176/appi.ajp.2015.14091178. From the University of Connecticut Health Center, West Hartford; and other institutions. **Funded by the NIMH. The authors declared no competing interests.**

***See Reference Guide.**

Childhood Abuse and Neurofunctional Abnormalities

Functional MRI (fMRI) studies showed slower error processing and increased activation of brain regions involved in error processing in young people with a history of severe physical abuse, compared with both psychiatric and healthy controls. These differences may arise from the need of abused children to constantly monitor their actions to avoid punishment.

Background: Deficits in cognitive control have been reported in patients with a history of childhood abuse or maltreatment. Ability to correctly detect errors and adjust behavior accordingly may be particularly important in abusive settings where punishment for mistakes is often harsh. However, research has suggested that persistent harsh punishments may sensitize a child to errors and lead to an overactive error-monitoring system.

Methods: Study participants were 22 medication-free young people, aged 13–20 years, referred from social services or psychiatric clinics. These patients had a history of severe childhood abuse, as determined by the Childhood Trauma Questionnaire and reports from the referring agency. Those with a history of sexual abuse were excluded because that type of abuse has different effects on brain structure and function. The study also included 2 comparison groups: 27 healthy control subjects from a similar socioeconomic background, and 17 young people with similar psychiatric comorbidity, including PTSD from non-abuse-related trauma. fMRI data were acquired during the stop task, in which the subject inhibits motor responses to go signals followed by unpredictably timed stop signals. The test was designed to elicit errors 50% of the time.

Results: Study participants had a mean age of 17 years. Those with a history of abuse had a somewhat lower IQ than both comparison groups, as expected because they had suffered the known cognitive consequences of their abuse. PTSD was present in 13 patients who had experienced abuse and in 12 psychiatric controls; depression and anxiety were also common in these groups.

Participants with a history of abuse had significantly slower responses on both go-signal reaction time and post-error reaction time than healthy controls ($p<0.05$). For failed inhibition trials, compared with healthy controls, abused young people also had significantly increased activation of error-processing regions of the dorsomedial frontal cortex, a large cluster comprising the left and right pre-supplementary and supplementary motor area, dorsal anterior cingulate cortex, and superior frontal gyri, as well as the left paracentral lobule. Compared with psychiatric controls, the abused subjects had increased activation in a smaller cluster in the supplementary motor area. Patterns of brain activation did not differ between the 2 control groups. The 3 groups did not differ in brain activation following successful trials, which suggests the functional abnormalities were specific to error processing. The results were robust in additional analyses that were conducted separately to adjust for IQ, psychopathology, and demographic factors.

Lim L, Hart H, Mehta M, Simmons A, et al: Neural correlates of error processing in young people with a history of severe childhood abuse: an fMRI study. *American Journal of Psychiatry* 2015;172 (September):892–900. From Kings College London, U.K.; and other institutions. **Funded by the National Medical Research Council; and other sources. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors disclosed no competing interests.**

Antidepressant Study Flawed

An independent reanalysis of data from an industry-sponsored controlled trial of paroxetine in adolescent depression has overturned the trial's major conclusion of efficacy and revealed higher-than-reported rates of serious adverse effects.[1]

Background: The trial data, published 14 years ago, were reanalyzed as part of the "restoring invisible and abandoned trials" (RIAT) initiative, started by an international group of researchers who believe there is a need to correct misleading reporting. RIAT researchers identified Study 329 as a misreported trial in need of restoration. The study, which claimed superior efficacy of paroxetine and imipramine compared with placebo, was conducted by SmithKline Beecham and published in the *Journal of the American Academy of Child and Adolescent Psychiatry* in 2001.[2]

Methods: For the reanalysis, the RIAT investigators used data from the clinical study publicly available on the manufacturer's website, other publicly available documents, and individual participant data provided by the manufacturer on a private website. The data were reanalyzed, for the most part using methods set out in the original study protocol. The study recruited 275 adolescents, aged 12–18 years, with DSM-III-R major depression of ≥8 weeks' duration. Patients were randomly assigned to receive flexibly-dosed paroxetine, imipramine, or placebo for 8 weeks. The study had 2 primary efficacy outcomes: change from baseline in the Hamilton Rating Scale for Depression (HAM-D) total score; and response, defined as a ≥50% reduction in the HAM-D or a score of ≤8.

Results: The protocol-specified analysis plan called for computation of an omnibus statistic for the overall significance of results for the 2 primary outcomes in all 3 treatment groups, followed by pairwise testing between treatments only if the omnibus statistic was significant. The RIAT investigators found that the omnibus statistic was not significant—there was no difference among the effects of 2 antidepressants and placebo—therefore, pairwise comparisons were not warranted. In the original publication and the clinical study report, the investigators did not

report the omnibus statistic but analyzed 2 of the 3 possible pairwise comparisons, finding significant differences between paroxetine and placebo and between imipramine and placebo. The original investigators set a prespecified threshold of 4 HAM-D points as signaling a clinically significant difference between treatments. The mean HAM-D decreased by 10.7 points with paroxetine, 9.0 with imipramine, and 9.1 with placebo.

The RIAT investigators also found no difference among treatments for any of the protocol-specified secondary endpoints. The original investigators found significant differences between treatments for 4 outcome variables that were not specified in the original analysis plan.

Significant underreporting of adverse events was also found in the re-analysis. Data from the patient-level forms were simply not transcribed into the adverse event listings in the clinical study report or were miscoded, resulting in underreporting of "serious, severe, and suicidal adverse events," the RIAT investigators say.

Editorial. Few studies have received as much criticism as Study 329.[3] It was deemed a "failed trial" by an FDA reviewer, yet used aggressively in the marketing of paroxetine. Failure to retract the publication has been attributed to the journal, the manufacturer, the American Academy of Child & Adolescent Psychiatry–whose ethics committee lacks a mandate to investigate misconduct, and Brown University–the principal research institution.

[1]Le Noury J, Nardo J, Healy D, Jureidini J, et al: Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ* 2015; doi 10.1136/bmj.h4320. From Bangor University, Wales, U.K.; and other institutions. **The Original Study 329 was funded by SmithKline Beecham. The reanalysis was conducted without specific funding. Some of the authors reported potential conflicts of interest.**

[2]Keller M, et al: Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 2001;40:762–772. See *Child & Adolescent Psychiatry Alerts* 2001;3(October):56.

[3]Doshi P: No correction, no retraction, no apology, no comment: paroxetine trial reanalysis raises questions about institutional responsibility (Feature). *BMJ* 2015; doi 10.1136/bmj.h4629. The author is an associate editor of *BMJ*.

Drug Trade Names*: imipramine—*Tofranil*; paroxetine—*Paxil

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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.

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.

Number Needed to Treat: 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.

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Therapeutic Equivalence of Generic *Concerta*

Children and adolescents with ADHD experienced significant symptom improvement when they were switched from a non-OROS to the OROS generic formulation of extended-release methylphenidate (*Concerta*).[1] This observation supports the FDA's concerns about the therapeutic inequivalence of generic *Concerta* formulations.

Background: *Concerta's* osmotic controlled-release oral delivery system (OROS) is a delivery technology designed to release methylphenidate from the capsule over 10–12 hours, consistent with the effect of 3-times-a-day dosing of immediate-release methylphenidate. Of 3 *Concerta* generics now on the market, only 1 uses OROS technology. This formulation is manufactured by Janssen, the manufacturer of brand-name *Concerta*, and marketed by Actavis under a licensing agreement. Two other extended-release generics, manufactured by Kremers and Mallinckrodt, are FDA-approved as pharmaceutical equivalents of *Concerta*, with the same dosage and route of administration. However, following reports from consumers of waning efficacy during the day, the FDA lowered the equivalence rating of these 2 generics in November 2014.[2] They are still approved but no longer recommended as automatically substitutable for *Concerta*.

Methods: Outcomes were compared among extended-release methylphenidate formulations in children and adolescents referred to an outpatient clinic at an academic medical center. All treatment decisions were made as part of routine clinical care. Following a diagnosis of ADHD (DSM-IV-TR), the patients were given a prescription for and were taking *Concerta*, but they were experiencing symptoms during the day, despite dosage titration. After contacting the pharmacies, it was discovered that non-OROS generics had been substituted. Patients' caregivers and pharmacists were then instructed to fill the prescriptions only with the OROS generic. Treatment efficacy was assessed using the Conners-Third Edition: Parent Rating Scale, Short Form [Conners 3-P(S)] at the time of diagnosis, following treatment with non-OROS generics, and again following treatment with the OROS generic.

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Results: The sample consisted of 14 patients, with an average age of 11 years (range 8–16 years). All patients had clinically significant scores on the Connors 3-P(S) Inattention subscale at baseline. Overall scores on the Conners 3-P(S) did not improve after treatment with the non-OROS generics, but they improved significantly when patients were switched to the OROS generic (p=0.0004 vs. baseline). Compared with scores during non-OROS treatment, after switching, Inattention scores were significantly reduced (p=0.014 for patients with inattentive-type ADHD and p=0.0015 for those with combined type). In patients with the combined type, scores on the Hyperactivity scale were also reduced (p=0.0048). Average scores on both subscales were below the clinically significant threshold when patients were receiving the OROS generic.

Discussion: The authors note that these observations are preliminary. The FDA is now conducting or concluding bioequivalence and pharmacokinetic/pharmacodynamic studies in healthy adults and in children with ADHD.

[1]Lally M, Kral M, Boan A: Not all generic Concerta is created equal: comparison of OROS versus non-OROS for the treatment of ADHD. *Clinical Pediatrics* 2015; doi 10.1177/0009922815611647. From the Medical University of South Carolina, Charleston. **This study was conducted without funding. The authors declared no potential conflicts of interest.**

[2]Methylphenidate hydrochloride extended release tablets (generic Concerta) made by Mallinckrodt and Kudco. FDA News Release available at www.fda.gov/Drugs/DrugSafety. See *Child and Adolescent Psychiatry Alerts* 2014;16 (November):61.

Depression Prevention in At-Risk Adolescents

Adolescents at familial risk of depression who completed a cognitive-behavioral prevention (CBP) program in a multi-center controlled trial continued to maintain lower rates of new-onset depression than a control group after 6 years of follow-up.[1]

Background: Previously reported results for this study sample indicate efficacy of CBP for acute treatment as well as shorter-term follow-up.[2,3] The present long-term follow-up study was designed to evaluate the extent and duration of those positive effects during the transition from adolescence to young adulthood.

Methods: Participants were 316 adolescents, aged 13–17 years at study entry, who had ≥1 parent with major depression or dysthymia either occurring in the past 3 years, with ≥3 years' duration, or with ≥3 recurrences. Adolescents themselves were not experiencing a depressive episode at study entry but had either a past depressive episode now in remission or current subsyndromal depressive symptoms. Participants were randomly assigned to a usual-care comparison group or to CBP, a modified version of the Coping with Depression for Adolescents program that emphasizes cognitive restructuring and problem solving. CBP consisted of 8 weekly 90-minute group sessions, 6 monthly booster sessions, and 2 informational sessions for the parents. Outcomes for the present analysis were measured at 75 months and included time to depression onset (the primary outcome), depression-free days, functioning (Global Assessment Scales), and developmental competence in emerging adulthood (Status Questionnaire).

Results: At 6 years, 88% of the original participants were available for follow-up. Their mean age was 21 years (range, 18–25 years). Depression onset was significantly less likely in the group that received CBP (hazard ratio,* 0.76; p=0.05). The groups did not differ statistically in the overall number of depressive episodes or depression-free days during follow-up. Further analysis indicated that CBP was effective prevention only in adolescents whose parents had not been experiencing a depressive episode at baseline.

The overall between-group differences were driven by lower depression onset in the CBP group early after treatment. Depression incidence was significantly lower during the first 9 months of follow-up in patients who received CBP (hazard ratio, 0.64; p=0.05), but not thereafter. Thus, gains were maintained but did not increase over the following years. CBP was not associated

with differences in use of mental health services, global functioning, or developmental competence. As with depression onset, the benefits in developmental competence were limited to adolescents whose parent was not experiencing a depressive episode at baseline.

Discussion: The acute and long-term effects of the CBP intervention in this study suggest it is beneficial. It is possible that the program might be made even more effective by treating parental depression either before or at the start of child treatment. Rather than focusing strictly on the adolescent, CBP programs could also work on improving parenting and the quality of the parent-child relationship. Additional booster sessions could potentially extend the early benefits of CBP over a longer time.

[1]Brent D, Brunwasser S, Hollon S, Weersing V, et al: Effects of a cognitive-behavioral prevention program on depression 6 years after implementation among at-risk adolescents: a randomized clinical trial. *JAMA Psychiatry* 2015; doi 10.1001/jamapsychiatry.2015.1559. From the University of Pittsburgh, PA; and other institutions. **Funded by the NIMH; and other sources. One study author disclosed potentially relevant financial relationships; the remaining 11 authors declared no competing interests.**

[2]Garber J, et al: Prevention of depression in at-risk adolescents: a randomized controlled trial. *JAMA 2009;301:2215–2224.*

[3]Beardslee W, et al: Prevention of depression in at-risk adolescents: longer-term effects. *JAMA Psychiatry* 2013;70:1161–1170.

***See Reference Guide.**

Aripiprazole Monotherapy for Resistant OCD

According to results of a preliminary study, aripiprazole monotherapy is effective in children with treatment-resistant obsessive-compulsive disorder.

Methods: Study subjects were 16 consecutively-treated children (mean age, 11 years) who had received aripiprazole monotherapy after showing no improvement with trials of cognitive behavioral therapy with ≥2 types of SSRI or clomipramine. Patients with schizophrenia or bipolar disorder were excluded from the retrospective analysis, but those with other psychiatric comorbidity were included. All patients received flexibly-dosed, open-label aripiprazole for 12 weeks and were evaluated for response and adverse effects monthly. The mean aripiprazole dosage was 4.75 mg/day (range, 2–7.5 mg/day).

Results: At baseline, patients were rated at least "markedly ill" according to scores on the Clinical Global Impression–Severity (CGI-S) scale. More than 80% of patients had comorbid disorders, most commonly ADHD, but also tics, major depression, conduct disorder, and/or oppositional defiant disorder.

After 3 months of treatment, patients showed substantial improvement in OCD symptoms and overall illness severity. (See table.) In addition, improvement in each of the 10 symptom domains of the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) was highly significant (p=0.002 or better). Only 1 patient experienced an adverse event, increased appetite.

Baseline and Follow-Up Evaluations			
CY-BOCS, mean	**Baseline**	**3 months**	**P value**
Obsession score	14.1	7.2	0.001
Compulsion score	16.4	7.6	<0.001
Total score	30.6	15.3	<0.001
CGI–Improvement, Number (Percent)			
No change or minimally improved	3 (19%)		
Significantly improved	5 (31%)		
Nearly or completely cured	8 (50%)		

Discussion: Aripiprazole augmentation has been shown to be effective in refractory OCD in several clinical trials, but there is less evidence of its efficacy as monotherapy. Its pharmacological profile, with a partial agonistic effect on D_2 receptors and 5-HT_{1a} agonistic properties, may underlie its efficacy as single-agent therapy for OCD.

Ercan E, Ardic U, Ercan E, Yuce D, et al: A promising preliminary study of aripiprazole for treatment-resistant childhood obsessive-compulsive disorder. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (September):580–584. From Ege University School of Medicine, Izmir, Turkey. **The study was conducted without funding. One author disclosed relationships with commercial sources; the remaining 4 authors declared no conflicts of interest.**

Common Drug Trade Names*: aripiprazole—*Abilify*; clomipramine—*Anafranil

Methylphenidate/Acetaminophen Hallucinations

A 6-year-old boy with ADHD had been receiving 18 mg/day OROS methylphenidate (*Concerta*) for 2 months with significant improvement in behavior. The only reported adverse effect was appetite suppression. He presented with a 1-week history of anxiety, fearfulness, and refusal to leave his parents. After he started 120 mg/day acetaminophen suspension following a flu-like illness, the patient reported visual hallucinations, during which he was oriented to time and place. Because hallucinations had not occurred with methylphenidate monotherapy, it was presumed not to be the cause. The acetaminophen was discontinued, and the hallucinations resolved. They did not recur during 6 months of follow-up with continued methylphenidate monotherapy.

Methylphenidate is generally safe and well tolerated but has reportedly caused psychotic symptoms in a small number of young patients. Because the patient was not rechallenged with the methylphenidate–acetaminophen combination, it is unclear whether the acetaminophen alone or the combination of the drugs precipitated the hallucinations. However, it was speculated that concomitant use of acetaminophen and methylphenidate led to excessive brain levels of dopamine that then resulted in the hallucinations. It is also possible that acetaminophen elevated the patient's serum methylphenidate concentrations, increasing the risk of adverse effects.

Herguner S, Ozayhan H: Visual hallucinations with methylphenidate and acetaminophen in combination. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (September):598–599. From Necmettin Erbakan University, Konya; and Konya Training and Research Hospital, Turkey. **The authors declared no competing interests.**

Cardiovascular Safety of Atypicals with Stimulants

Concomitant use of atypical antipsychotics did not increase the cardiovascular risks of long-acting stimulants in children and adolescents with ADHD, according to a population- based study.

Background: Clinical trials have shown that stimulants lead to increases in heart rate and blood pressure, but recent observational studies and a meta-analysis have not shown increased risk of disease events. Antipsychotics, used increasingly to manage behavioral symptoms of ADHD and comorbid disorders, are associated with orthostatic hypotension, QT interval prolongation, transient ischemic attack, stroke, and myocardial infarction (MI).

Methods: Claims data were collected for a 4-year period from the IMS LifeLink database, which contains information about commercially insured patients in the U.S. The study cohort consisted of nearly 38,000 young patients, aged 6–16 years, with a diagnosis of ADHD who received a new prescription for a long-acting stimulant between July 2004 and December 2006. Medications of interest included 5 long-acting stimulants (i.e., methylphenidate, dexmethylphenidate, amphetamine–dextroamphetamine, pemoline, lisdexamfetamine) and 6 second-generation antipsychotics (i.e., clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole). Concomitant use was defined as receiving both types of medication at the same time for ≥14 days. Patients' records were examined for up to 1 year from the first

stimulant prescription or until they switched to a shorter-acting stimulant class. The primary outcome was a cardiovascular disease event—e.g., acute MI, stroke, hypertension, angina, aneurysm, arrhythmia, syncope, tachycardia, or palpitation.

Results: Of the nearly 38,000 patients who received treatment with a long-acting stimulant, 538 (2%) also received an atypical antipsychotic. Those who used both classes of medication were predominantly male (71%), aged ≤12 years (64%), and privately insured (94%). There was no difference in risk for a cardiovascular event between users and nonusers of atypical antipsychotics (adjusted hazard ratio,* 1.19). Cardiovascular risk was increased in boys, patients aged ≤12 years, and those with comorbid tic disorders, asthma, diabetes, and obesity, but the association was independent of combined use of the 2 medication classes. Risk was also increased in patients taking mood stabilizers and/or anxiolytics at baseline.

Discussion: Although both classes of medication have been associated with cardiac risk, their opposing pharmacological actions may cause them to counteract each other's adverse-event profile, thus not increasing cardiac risk. Until additional evidence is produced, cardiovascular-risk screening should be undertaken every 3 months if a long-acting stimulant and an atypical antipsychotic are used concurrently.

Bali V, Kamble P, Aparasu R: Cardiovascular safety of concomitant use of atypical antipsychotics and long-acting stimulants in children and adolescents with ADHD. *Journal of Attention Disorders* 2015; doi: 10.1177/1087054715608443. From Westlake Village, CA (independent practice); and other organizations. **This research was conducted without funding. The authors declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; clozapine—*Clozaril*; dexmethylphenidate—*Focalin*; lisdexamfetamine—*Vyvanse*; methylphenidate, long acting—*Concerta*; amphetamine-dextroamphetamine—*Adderall*; olanzapine—*Zyprexa*; pemoline (not available in the U.S.)—*Cylert*; quetiapine—*Seroquel*; risperidone—*Risperdal*; ziprasidone—*Geodon

***See Reference Guide.**

Paliperidone ER: Long-Term Safety

Treatment with extended-release paliperidone was generally well tolerated over 2 years in adolescents participating in a large open-label extension study.

Methods: This study was conducted to assess the safety and tolerability of paliperidone and, as a secondary objective, to measure efficacy. Participants were aged 12–17 years at enrollment and had a confirmed DSM-IV diagnosis of schizophrenia. The 400 study patients were enrolled either directly (n=243) or after participating in a 6-week placebo-controlled trial of paliperidone (n=157). Open-label paliperidone was initiated at 6 mg/day and could be adjusted to dosages between 1.5 and 12 mg/day based on efficacy and tolerability.

Results: A total of 220 participants completed the 2-year study, and the average duration of paliperidone exposure was >15 months. The most common paliperidone-associated adverse events were somnolence and weight gain (18% each). Severe treatment-emergent adverse events occurring in ≥3 patients were schizophrenia exacerbation (n=19), suicidal ideation (n=8), dystonia (n=4), weight gain (n=4), akathisia (n=3), and anxiety (n=3). A total of 25 patients (6%) discontinued treatment because of adverse events.

There were no clinically significant changes in pulse rate, blood pressure, or electrocardiogram parameters. Nearly half of patients gained >7% of their initial body weight, but z scores* indicated that the weight gain was usually age-appropriate. About 17% had a clinically meaningful weight gain in relation to their z score. Most patients were post-pubertal at study entry, but those who started treatment at age 12 or 13 years experienced normal sexual maturation.

Lipid levels remained stable over time, but 14 patients (4%) demonstrated a shift from low or normal to high levels of glucose. Serum prolactin increased with treatment, reaching above-normal values in 60% of boys and 48% of girls. Prolactin-related adverse effects (mainly

amenorrhea and galactorrhea in girls) occurred in 9% of patients, including 4 who discontinued paliperidone as a result. Treatment-related extrapyramidal symptoms affected 37% of patients and included akathisia (13%), tremor (11%), muscle rigidity (6.5%), and dystonia (5%). No cases of tardive dyskinesia were reported.

Treatment efficacy was measured using the Positive and Negative Syndrome Scale (PANSS). Total PANSS scores improved during the first 3 months of treatment and remained stable thereafter. A total of 67% were considered treatment responders, and 42% achieved remission.

Discussion: Although atypical antipsychotics have similar efficacy, their adverse-effect profiles differ. This study suggests paliperidone is associated with less weight gain than risperidone or olanzapine and a low risk of hyperglycemia, similar to risperidone. Extrapyramidal symptoms were more common in this patient population than in adults taking paliperidone, an observation common to other antipsychotics. Similar to risperidone, paliperidone increases prolactin levels, but this does not appear to affect Tanner stage progression.

Savitz A, Lane R, Nuamah I, Singh J, et al: Long-term safety of paliperidone extended release in adolescents with schizophrenia: an open-label, flexible dose study. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (September): 548–557. From Janssen Research & Development, LLC, Titusville, NJ. **Funded by Janssen Research & Development, LLC. All study authors declared financial relationships with commercial sources, including Janssen**.

Common Drug Trade Names*: olanzapine—*Zyprexa*; paliperidone—*Invega*; risperidone—*Risperdal

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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 1 group has half the risk of the other group.

Z Score: A statistical measurement of a score's relationship to the mean in a group of scores. A Z-score of 0 means the score is the same as the mean.

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Chewable Methylphenidate ER

The FDA has granted approval for the first chewable formulation of extended-release methylphenidate (*QuilliChew ER*). In a clinical trial of children aged 6–12 years with ADHD, *QuilliChew* improved both attention and behavior beginning 45 minutes after ingestion and lasting through an 8-hour laboratory classroom challenge. The new formulation, for use in patients aged ≥6 years, will be available in 20-, 30-, and 40-mg tablets that can be taken with or without food and is expected to be in pharmacies in the first quarter of 2016. The recommended starting dosage is 20 mg/day and dosages >60 mg/day are not recommended. As with other stimulants, patients should be evaluated for cardiac disease before starting treatment with *QuilliChew* and use is contraindicated with concurrent or recent MAOI use. *QuilliChew* contains phenylalanine, which can be harmful to patients with phenylketonuria. Adverse effects appear to be similar to other methylphenidate formulations.

Pfizer receives U.S. FDA approval of new QuilliChew ER (methylphenidate hydrochloride) extended-release chewable tablets CII [press release]. New York, NY: Pfizer; December 7, 2015. Http://on.pfizer.com/1HQNOeg.

Technology-Assisted CBT for Adolescent Depression

A technology-enhanced program was useful in training therapists in cognitive behavioral therapy for adolescent depression and in enhancing the therapeutic alliance.

Background: The present study was conducted by the developers of the technology-enhanced CBT protocol (available at http://telepsychology.net/default.aspx) and funded by the NIMH as part of the institute's initiative to develop technological enhancements of evidence-based treatments. The online training module was developed to address "a critical shortage of CBT-trained therapists."

Methods: The study recruited 18 clinicians without prior accreditation or formal training in CBT. Each clinician was randomly assigned to either CBT or their usual treatment methods, and each provided treatment for 4 adolescents recruited from his or her practice for 12 weeks

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using CBT or usual methods. The enhanced-CBT protocol had 3 components: therapist training, in-session use of tablet computers to convey CBT concepts and skills, and between-session text messaging for homework reminders and self-monitoring. The training consisted of an online tutorial based on the NIMH manual for CBT in adolescent depression and took an average of about 5.5 hours to complete. Trained therapists were then given a tablet with access to materials for use with patients. Between-session text reminders were sent with a timing and frequency set collaboratively by the patient and clinician, typically twice a day. The primary clinical outcome measure was the patient-reported Quick Inventory of Depressive Symptomatology—Adolescent (QIDS-A). Other outcome measures were a pre- and post-test of CBT principles for the clinician and standardized measures of user satisfaction and the therapeutic alliance for both clinician and patient.

Results: After participating in the online training tutorial, clinicians demonstrated a significant ($p<0.001$) increase in knowledge of CBT concepts, and virtually all of the program's 23 specified learning objectives were met. Clinicians gave the program high ratings for clarity, usefulness of content, and user-friendliness and said that they were likely to recommend it to others. Clinicians also gave good-to-excellent ratings to various aspects of the in-session teaching materials. Among adolescents, ≥85% said that the in-session materials and text messaging were helpful in learning new material and enhancing the effectiveness of homework.

Mean scores on the QIDS-A showed improvement in depressive symptoms, which were numerically but not statistically larger in adolescents who received CBT, with a small effect size* (0.08) relative to treatment as usual. The therapeutic alliance was rated significantly higher with CBT than treatment as usual among both patients ($p=0.03$) and clinicians ($p=0.001$).

Discussion: This study demonstrates the feasibility of technology-assisted CBT as an enhancement of existing treatment, rather than as a lower-intensity replacement designed to save therapists' time, as with recent technology-based stepped-care models. The small-but-real effect size should be viewed as encouraging, possibly suggesting a need for additional in-person CBT training. The improvement in therapeutic bond with the technology could help keep adolescents in treatment.

Kobak K, Mundt J, Kennard B: Integrating technology into cognitive behavioral therapy for adolescent depression: a pilot study. *Annals of General Psychiatry* 2015; doi 10.1186/s12991-015-0077-8. From the Center for Telepsychology, Madison, WI; and the University of Texas Southwestern Medical Center, Dallas. **Funded by the NIMH; and other sources. All study authors declared relevant financial relationships.**

***See Reference Guide.**

Parent Interventions for Disruptive Behavior

Psychosocial interventions for childhood disruptive behavior disorders are most effective when they include a parent component, according to a systematic review and meta-analysis of comparative studies.

Background: The use of outpatient psychotherapy for childhood behavior disorders is declining, and medication-only approaches are increasing. While this trend may reflect changes in reimbursement, it is also possible that it is the result of decreasing satisfaction with available psychosocial therapies. The present study was undertaken to explore the overall effectiveness of these therapies as well as to compare the effects of various components.

Methods: A comprehensive literature search identified controlled trials, not necessarily randomized, of psychosocial treatments for primary behavior disorders in children. Eligible studies for the network meta-analysis* were those that reported results using at least 1 of the 3 most common parent-reported outcome measures: the Eyberg Child Behavior Inventory (ECBI) Intensity subscale; the ECBI Problem subscale; or the Child Behavior Checklist Externalizing

subscale. Interventions were broadly classified as control (treatment as usual or wait-list), treatments with only a child component, those with only a parent component, or multicomponent interventions.

Results: A total of 66 studies were included in the systematic review. Of these, 2 examined child-only interventions, 25 parent-only interventions, and 39 multicomponent interventions; 28 of these studies met criteria for inclusion in the meta-analysis. The most common named interventions were the Incredible Years, Parent-Child Interaction Therapy, the Positive Parenting Program, and Multisystemic Therapy.

Child-only, parent-only, and multicomponent interventions were all superior to the control condition. Reductions in disruptive symptom scores were 1.2 standard deviations for both parent-only and multicomponent interventions, compared with 1.0 standard deviation for child-only interventions. The investigators also calculated the probability of each treatment being the most effective. The probability was 43% for both parent-only and multicomponent programs and 14% for child-only programs. However, there was too little evidence to conclude that child-only programs are inferior. Treatment was slightly more effective in preschool children than in older age groups.

Discussion: The interventions studied in this meta-analysis were provided in academic settings, and the results may not be generalizable to clinical practice in the community. In addition, the studies did not address concurrent use of medication. As a result, additional study appears to be warranted.

Epstein R, Fonnesbeck C, Potter S, Rizzone K, et al: Psychosocial interventions for child disruptive behaviors: a meta-analysis. *Pediatrics* 2015;136 (November):947–960. From Vanderbilt University, Nashville, TN. **Funded by the Agency for Healthcare Research and Quality. The authors declared no conflicts of interest.**

***See Reference Guide.**

Behavioral Activation and Multimodal Treatment

In a randomized controlled trial, SSRI-related activation syndrome hindered the efficacy of cognitive behavioral therapy (CBT) in pediatric obsessive-compulsive disorder (OCD).

Methods: Study subjects were 56 children and adolescents, aged 7–17 years, with a primary diagnosis of OCD. Participants received randomized drug therapy with either sertraline (*Zoloft*), titrated on a regular or slow schedule, or placebo. Regular titration was 25–200 mg/day over 9 weeks on a flexible schedule, and slow titration had the same target and duration but proceeded according to fixed increments. The optimal dose was reached at week 4 with regular titration and week 8 with slow titration. After 4 weeks of drug or placebo treatment, all participants began weekly CBT with exposure and response prevention.

SSRI-associated activation was measured using a recently validated scale created by the study research team: the Treatment-Emergent Activation and Suicidality Assessment Profile (TEASAP). This parent-rated instrument consists of 38 items in 5 symptom clusters: irritability; akathisia/hyperkinesis/somatic anxiety; disinhibition/impulsivity; mania; and self-injury/suicidality/harm to others. Scores were classified as low, average, and high, with cutoffs 1 standard deviation above and below the mean. Only activation symptoms that developed during treatment were included in the analysis. Treatment efficacy was assessed using the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

Results: The average daily sertraline dose was 76 mg for the slow titration group and 148 mg for the regular titration group. Activation symptoms appeared most frequently during the transitions from no treatment to 25 mg/day and from 50 to 75 mg/day. Response, defined as a ≥50% improvement in CY-BOCS score, occurred in 40% of the sample. Activating symptoms

were predictive of a lack of response; response occurred in 74% of those with low levels of activation symptoms, 37% of those with average levels of activation symptoms, and 5% of those with high levels of activation symptoms. Fluctuations in activation symptoms were predictive of fluctuations in OCD symptoms on a session-to-session basis. Among the TEASAP subscales, OCD symptoms varied in relation to irritability, akathisia, and disinhibition, but not mania or suicidal ideation. Only variations in irritability predicted OCD symptom outcomes on a session-to-session basis. Average higher doses of sertraline were associated with lower OCD symptom severity. However, in a multivariate model, controlling for sertraline dosage did not affect the relationship between activation symptoms and treatment outcomes.

Discussion: Estimates of the incidence of activation symptoms with SSRIs vary widely, in part because of the lack of a standardized assessment measures. This study is notable as the first to use such an instrument. The results indicate that activation symptoms, and particularly irritability, may slow treatment gains. Possible reasons include direct negative effects of activation symptoms on the therapeutic process by disrupting the therapeutic relationship; reducing motivation; increasing disinhibition; or acting via indirect mechanisms such as sleep interference.

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

Reid A, McNamara J, Murphy T, Guzick A, et al: Side-effects of SSRIs disrupt multimodal treatment for pediatric OCD in a randomized-controlled trial. *Journal of Psychiatric Research* 2015;71 (December):140–147. From the University of Florida, Gainesville; and other institutions. **Funded by the NIMH. Three of the 7 study authors disclosed financial relationships with commercial sources.**

***See Reference Guide.**

Patient Opinions of ECT

Patients with schizophrenia spectrum disorders who had received ECT as adolescents generally had a positive opinion of the treatment, according to a questionnaire-based study. Patients with the same disorders who did not receive ECT reported less knowledge about the treatment, but they did not have negative views of it.

Methods: Questionnaires were administered to all available patients with schizophrenia or schizoaffective disorder who had received treatment with ECT while under age 18 years at a research hospital in Spain in 2003–12. ECT use was approved by a committee in each case, according to American Academy of Child and Adolescent Psychiatry (AACAP) guidelines. Of 33 patients who underwent treatment, 19 could be reached and completed the questionnaire assessing their knowledge, attitude, and experience with ECT. A comparison group of 21 patients, who received antipsychotic medications only, also completed a questionnaire about general attitudes toward medication.

Results: Patients had a mean age of 21 years at the time of assessment. All were outpatients, most were taking medication, and none was currently receiving ECT. Of the ECT group, 90% said they currently felt better than they had around the time when they received ECT. Most patients did not remember the treatment well or at all. Most of them thought they were receiving ECT to treat their disorder, and none thought it was given as punishment or to control unacceptable behavior.

Of the 19 patients, 15 (79%) felt that ECT had helped them, 3 did not know or remember, and 1 felt it had not helped; no patient felt it made them worse. About one-third were very scared before the first ECT session, and almost half felt it was more frightening than having something done at the dentist. The most commonly reported adverse effects were confusion, headache, and nausea; 8 patients reported memory problems with ECT, but 5 also reported memory problems with medication and 4 believed both ECT and medication had improved their memory. Most patients did not try to hide the fact that they had ECT from others. A total

of 13 patients felt their illness was worse than the ECT treatment, 1 felt ECT was worse, and 4 had no opinion. Patients in the ECT group were more likely than controls to report that ECT was a safe treatment. Most patients in both groups said they would accept ECT in the future if it was recommended.

Discussion: AACAP indications for ECT use in adolescents with schizophrenia spectrum disorders are the same as in adults: psychotropic drug resistance, medication intolerance, contraindication to medication, or a specific clinical indication (e.g., catatonia, neuroleptic malignant syndrome). Although it has been shown to be safe and effective in adolescents, use of ECT in young patients is limited. The limited evidence, however, suggests positive attitudes toward ECT. The positive attitudes of adolescents who undergo ECT could be helpful in counteracting some of the stigma associated with the treatment.

Flamarique I, Castro-Fornieles J, de la Serna E, Pons A, et al: Patients' opinions about electroconvulsive therapy: what do adolescents with schizophrenia spectrum disorders think? *Journal of Child and Adolescent Psychopharmacology* 2015;25 (October):641–648. From the Hospital Clinic of Barcelona, Spain; and other institutions. **Funded by the government of Catalonia; and other sources. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

Heart Rate and Violent Criminality

In a Swedish registry-based longitudinal study, low resting heart rate in boys during late adolescence was associated with increased risk of violent criminality, nonviolent criminality, exposure to assault, and unintentional injury in adulthood.[1]

Methods: Men born in Sweden between 1958 and 1991 who were evaluated at age 18 years for conscription into the country's military service (mandatory until 2009) comprised the study sample. Blood pressure and resting heart rate were measured as part of the conscription examination, and study subjects were classified into quintiles according to heart rate. The primary outcome was time to first criminal conviction for a crime either violent (e.g., murder, kidnapping, robbery, arson, sexual crimes) or nonviolent (e.g., drug, traffic, property offenses) between 1973 and 2009 (average length of follow-up, 18 years). Secondary outcomes were injuries believed to be the result of fearlessness or stimulation-seeking behavior, and being the victim of an assault. The statistical models were adjusted for a broad spectrum of variables including body size and cardiorespiratory fitness.

Results: The cohort consisted of >700,000 men, with an average heart rate of 72 beats per minute (bpm). The lowest quintile had heart rates of <60 bpm.

More than 40,000 men were convicted of a violent crime during follow-up. The quintile with the lowest resting heart rate had a statistically significantly elevated risk of all study outcomes compared with every other quintile. (See table.)

For specific types of crime, men in the lowest quintile had a hazard ratio of 1.67 for severe violent crime (i.e., those resulting in imprisonment or other custodial sentences) and 1.42 for less severe violent crime. Rates of sexual crime, however, were not related to heart rate in men who had no other convictions for violent crime. Low heart rate was associated with about a 30–40% increase in each category of nonviolent crime: drug-related, traffic, and property offenses.

Study outcomes in subjects with the lowest quintile of resting heart rate (35–60 bpm) vs. the highest quintile (reference group, 83–145 bpm).

Outcome	Hazard Ratio*
Violent crime	1.49
Nonviolent crime	1.33
Assault injuries (as victim)	1.41
Unintentional injuries (as victim)	1.31

Editorial.[2] Previous studies, with much smaller samples, have shown that low resting heart rate is predictive of antisocial behavior in children and adolescents. The present study firmly establishes the relationship and extends it into adulthood, and suggests that low heart rate may be a marker for broad rule-breaking behavior in general and a predictor of serious violence in particular. Potential explanations for the association include theories that low heart rate is a marker for fearlessness and impulsive stimulation seeking. Persons with these traits may tend to place themselves at risk, increasing their incidence of unintentional injuries and assaults.

[1]Latvala A, Kuja-Halkola R, Almqvist C, Larsson H, et al: A longitudinal study of resting heart rate and violent criminality in more than 700,000 men. *JAMA Psychiatry* 2015;72 (October):971–978. From the Karolinska Institutet, Stockholm, Sweden. **Funded by the Swedish Research Council for Health, Working Life and Welfare; and other sources. The authors reported no conflicts of interest.**

[2]Raine A: Low resting heart rate as an unequivocal risk factor for both the perpetuation of and exposure to violence [editorial]. *JAMA Psychiatry* 2015;72 (October):962–964. From the University of Pennsylvania, Philadelphia. **The author reported no conflicts of interest.**

***See Reference Guide.**

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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 1 group has half the risk of the other group.

Network Meta-Analysis: A statistic method that can provide estimates of efficacy for multiple treatment regimens, even when direct comparisons are unavailable. This method extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in ≥2 studies that have 1 treatment in common. For example, if in a clinical trial comparing treatment A with treatment B, option A is determined to be superior, and a separate trial in similar patients found option B superior to a third agent, option C, a network meta-analysis of these 2 trials would allow a researcher to conclude that treatment option A is more effective than option C, even though the 2 options have never been directly compared.

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 are posted at www.alertpubs.com.

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