

CHILD & ADOLESCENT PSYCHIATRY ALERTS

2017 Issue Collection

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New CME Activities Have Been Released . . . Are You Enrolled?

Internet-Delivered CBT for Anxiety Disorders

According to a follow-up study of children with anxiety disorders who participated in a randomized controlled trial,¹ internet-delivered cognitive behavioral therapy produced lasting improvement.²

Methods: Study participants were self-referred families with a child, aged 8–12 years, who had a primary diagnosis of generalized anxiety disorder, panic disorder, separation anxiety, social anxiety disorder, or a specific phobia. The study excluded children with a diagnosis of ADHD, autism, depression, or acute psychiatric conditions. Patients were randomly assigned to internet-delivered CBT or a wait-list control. Treatment consisted of a parent-led, exposure-based, 10-session program with online therapist support. Patients who still met diagnostic criteria in the control group were offered the active CBT at the end of the initial observation period. Treatment efficacy was measured at the end of therapy and at 3 and 12 months post-treatment using the Clinician Severity Rating, derived from the Anxiety Disorder Interview Schedule Child/Parent Version. An additional aim of the trial was to identify variables that might predict response. Potential moderators included comorbidity, depressive symptoms, and parental psychopathology. The 3-month evaluation was used to test the predictive factors, and the 12-month evaluation was the time point for the primary long-term efficacy comparison.

Results: A total of 84 children received internet-delivered CBT, either initially (46 children) or after crossing over from the control condition (38 children). At baseline, patients had an average of ≥ 3 anxiety-disorder diagnoses. Most had a principal diagnosis of separation anxiety or specific phobia, and about 20% had a principal diagnosis of generalized anxiety disorder. Of the families that started CBT, 83% completed ≥ 9 modules, including nearly all of the psycho-education components. Eight families sought additional help outside the study before the 12-month evaluation.

Internet-delivered CBT was associated with large improvements in anxiety-disorder symptoms at the end of treatment (effect size,* 1.33). Clinician Severity Rating scores decreased from 5.7 at

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baseline to 4.2 post-treatment ($p < 0.001$) and continued to decrease at the 3-month assessment (3.4; effect size vs post-treatment, 0.56) and 12-month assessment (2.8; effect size vs post-treatment, 0.42). At 3 months, 55% of the study children no longer met criteria for their principal diagnosis, and the rate increased to 73% at 12 months. One-third did not meet criteria for any anxiety disorder at 3 months, and 40% at 12 months. Secondary outcome measures, including global functioning and parent-rated anxiety, also showed improvement. A multivariate analysis identified only 1 factor that was predictive of treatment nonresponse: suspected autism spectrum disorder.

Discussion: Previous studies of internet-delivered CBT for childhood anxiety disorders have shown similar patterns of maintenance and even improvement of response. The finding that children with autism symptoms may be less likely to benefit from the therapy also replicates previous research.

¹Vigerland S, et al: Internet-delivered cognitive behavioral therapy for children with anxiety disorders: a randomized controlled trial. *Behavior Research and Therapy* 2016;76:47–56.

²Vigerland S, Serlachius E, Thulin U, Andersson G, et al: Long-term outcomes and predictors of internet-delivered cognitive behavioral therapy for childhood anxiety disorders. *Behaviour Research and Therapy* 2017;90 (March):67–75. From the Karolinska Institutet, Sweden; and other institutions. **Funded by the Stockholm County Council; and other sources. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

Prazosin for Nightmares in PTSD

The blood pressure lowering medication prazosin (*Minipress*) appears to be an effective treatment for nightmares related to posttraumatic stress disorder in children and adolescents, according to a systematic review.

Background: Sleep disturbances are common in children and adolescents who have recently suffered a traumatic event. Currently there are no FDA-approved medications for treating PTSD-related nightmares in children. Prazosin has been shown to be effective in randomized trials in adults with PTSD. It is a lipid-soluble α_1 adrenergic receptor antagonist and the only drug in its class that crosses the blood-brain barrier, where it decreases sympathetic activity in the brain. Nightmares and many of the other hyperarousal symptoms of PTSD are believed to arise from elevated noradrenergic responsiveness in the prefrontal cortex. In adults, symptoms of PTSD have been shown to improve significantly when sleep disturbance is treated.

Methods: A comprehensive literature search was undertaken to identify reports of prazosin use to treat PTSD-associated sleep disorders in children and adolescents. Bibliographic data from identified studies were also reviewed for additional publications.

Results: No reviews or clinical trials were identified in the search; the literature base comprised 6 case reports describing 7 patients, aged 7–16 years, who had experienced such traumas as abuse, parental neglect, sexual assault, and witnessing a friend's violent death. In most cases, nightmares persisted despite treatments, including cognitive behavioral therapy, supportive psychotherapy, melatonin, and first- and second-generation antidepressants from several classes. In some cases, these treatments ameliorated other PTSD symptoms, but nightmares persisted. Prazosin was administered in 1–4 mg doses at bedtime. In each case, the child experienced a marked reduction in both nightmare frequency and intensity. Improvements in sleep quality and in hyperarousal and intrusive PTSD symptoms were also evident. The only reported adverse effect was weight gain and increased body mass index in a boy who received treatment for 11 months. Two other patients had increases in nightmares after prazosin was discontinued, accompanied in 1 case by an increase in aggressive behavior.

Discussion: The reports in children indicate promise but provide little guidance for clinicians who would like to use prazosin to treat PTSD-related nightmares. Large randomized trials appear to be warranted.

Akinsanya A, Marwaha R, Tampi R: Prazosin in children and adolescents with posttraumatic stress disorder who have nightmares: a systematic review. *Journal of Clinical Psychopharmacology* 2017; doi 10.1097/JCP.0000000000000638. From MetroHealth Medical Center, Cleveland, OH. **Source of funding not stated. The authors declared no competing interests.**

Single-Session Interventions

Up to 80% of young people with psychiatric disorders do not receive treatment. Among those who do, dropout rates are high. Single-session interventions are gaining attention as a way of increasing access to treatment. According to the results of a systematic literature review and meta-analysis of 50 randomized controlled trials, single-session interventions were associated with an overall mean effect size* of 0.32 relative to control conditions ($p < 0.001$). Positive effects were largest for anxiety problems (effect size, 0.58) and conduct problems (effect size, 0.52). Effects were smaller but still significant for other problems such as low self-esteem or self-efficacy and for substance abuse. Effects were nonsignificant for depression and family relationship problems, in part because of small study samples. The effect for eating disorders was large but not statistically significant (effect size, 1.29).

The effects of single-session interventions did not differ according to whether the sample was clinically diagnosed or from the community, whether the intervention was for treatment or prevention, or whether the prevention was indicated, selective, or universal. Therapist-administered interventions had larger effects than self-administered ones (effect sizes, 0.33 and 0.21, respectively), although the difference was not statistically significant. Effects were largest when measured in the period immediately after the intervention to 2 weeks later and smallest when measured ≥ 13 weeks post intervention.

Study Rating*—89%: This study met most criteria for a systematic review/meta-analysis. However, the source of funding was not stated.

Schleider J, Weisz J: Little treatments, promising effects? Meta-analysis of single-session interventions for youth psychiatric problems. *Journal of the American Academy of Child and Adolescent Psychiatry* 2016; doi 10.1016/j.jaac.2016.11.007. From Harvard University, Cambridge, MA. **Source of funding not stated. One study author disclosed financial relationships with both commercial and noncommercial sources; the remaining author disclosed financial relationships with noncommercial sources.**

*See Reference Guide.

Amantadine for Aggressive Behavior

In a small series of hospitalized children, use of adjunctive amantadine reduced aggression and decreased the use of restraints and seclusion.

Background: Amantadine is an N-methyl-D-aspartate receptor antagonist that increases synaptic dopamine. According to previous reports, it has reduced aggression in children with neurodevelopmental disorders and has been used as an adjunct to risperidone in children with autism spectrum disorders and in patients with traumatic brain injury.

Methods: Charts from a single institution were retrospectively reviewed to identify psychiatrically-hospitalized children who had been started on amantadine for the management of aggressive behavior over a 2-year span. The 8 children (1 girl) ranged in age from 6 to 10 years. The most common primary diagnoses were ADHD, intermittent explosive disorder, oppositional defiant disorder, and bipolar disorder. Five children had borderline intellectual function or an unspecified cognitive disorder, and 4 had confirmed or suspected in-utero drug exposure. Previous or background medications included stimulants, second-generation

antipsychotics, mood stabilizers, alpha agonists, and antidepressants. Changes in aggressive behavior were evaluated by a child and adolescent psychiatrist using the Clinical Global Impression–Improvement (CGI-I) scale.

Results: The children were hospitalized for between 58 and 156 days (mean, 113 days) and received adjunctive amantadine for 20–92 days. On the CGI-I, 5 children were rated as "very much improved" and the other 3 as "much improved." Average seclusions per week were reduced from 1.8 at baseline to 0.25 during week 1 of treatment ($p=0.01$), and as-needed medications declined from 4 to 1.63 per week ($p=0.02$). In week 2, use of physical restraints was also significantly reduced from baseline (from 1.59 to 0 per week; $p=0.04$). During weeks 3 and 4, all 3 types of intervention were used fewer times per week than at baseline, but the differences were no longer statistically significant, possibly because of the small sample size. No patient was readmitted to the facility within 60 days following discharge, and only 1 was readmitted within 180 days. No adverse effects of amantadine were observed.

McGrane I, Loveland J, Zaluski H: Adjunctive amantadine treatment for aggressive behavior in children: a series of eight cases. *Journal of Child and Adolescent Psychopharmacology* 2016;26 (December):935–938. From Shodair Children's Hospital, Helena, MT; and the University of Montana Skaggs School of Pharmacy, Missoula. **This study was conducted without external funding. The authors declared no competing interests.**

Common Drug Trade Names: amantadine—*Symmetrel*; risperidone—*Risperdal*

Pathways to Major Depression in High-Risk Youth

A British longitudinal study of children and adolescents at high familial risk for major depression identified 6 mechanisms contributing to a first depressive episode, including 2—irritability and fear/anxiety—that may be amenable to clinical intervention and 2 others—poverty and psychosocial adversity—that are possible targets for community-based interventions.¹

Methods: Participating families were recruited from U.K. general practices and had 1 parent with ≥ 2 episodes of major depressive disorder. The youngest child between the ages of 9 and 17 years in each family was selected for follow-up. Parents and offspring were assessed on 3 occasions: at baseline, after about 16 months, and after another 12 months. The primary study outcome was the onset of major depressive disorder in the young person, measured using the Child and Adolescent Psychiatric Assessment (CAPA). Antecedent variables, assessed at baseline, were low mood (Mood and Feelings Questionnaire); fear/anxiety (Screen for Child Anxiety Related Emotional Disorders); irritability and disruptive behavior (subscales of the CAPA); familial risk of major depressive disorder (severity in the parent and occurrence in other family members); self-reports of stressful life events; and parent-reported household income.

Results: A total of 337 families participated, and nearly all parents with depression were mothers. Offspring had a mean age of 12 years at baseline, 140 were boys and 197 were girls. A total of 20 young people (including 14 girls) had a first episode of major depression during follow-up, with onset at a mean age of 14 years. Of the clinical antecedents, irritability and fear/anxiety were associated with depression onset ($p=0.03$ and $p<0.001$, respectively), but low mood and disruptive behavior were not. Both economic disadvantage and low socioeconomic status were directly associated with depression onset ($p=0.02$ and $p<0.001$), and both were also associated with the clinical antecedents.

Discussion: These results suggest that primary prevention of depression in young people with high familial risk should address irritability and fear/anxiety in the child and should also take social risk factors into account. Family-based programs may be indicated in this risk group, particularly in the U.S., where, according to an accompanying editorial,² women of childbearing

age have higher rates of depression and a greater burden of disease than British women; rates of violence (an aspect of adversity) are higher; adolescent depression is associated with greater disability; and there is a 4-fold higher rate of lethal self-harm.

¹Rice F, Sellers R, Hammerton G, Eyre O, et al: Antecedents of new-onset major depressive disorder in children and adolescents at high familial risk. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.3140. From Cardiff University, Wales U.K.; and other institutions. **Funded by the Sir Jules Thorn Charitable Trust; and other sources. The authors declared no competing interests.**

²Glowinski A, Rosen M: Prevention targets for child and adolescent depression [editorial]. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.3160. From Washington University School of Medicine, St. Louis, MO. **The authors declared no financial relationships with commercial sources.**

Child Psychiatric Access Projects

Most children in need of behavioral health treatment do not receive care. This is due in part to a lack of available services, and as a result, primary care physicians are assuming more responsibility for the mental health care of their patients. Child psychiatric access projects, now in place in 31 states and the District of Columbia, connect pediatricians, family physicians, and other clinicians with psychiatrists or other behavioral health specialists who provide brief telephone consultations on a case-by-case basis. Despite the success of these programs, concerns remain about the effectiveness of communications between primary-care and specialist providers.

The Five S's is a framework developed to provide a simple but comprehensive set of questions, to be reviewed by the primary care clinician before the specialist consultation. The framework does not require the primary care physician to reach a diagnosis before contacting the specialist. Rather, it is designed to help the physician collect the information that would be most useful to the mental health provider.

The Five S's

- **Safety:** Are there concerns about suicidal thought or intent or other safety concerns?
- **Specific Behaviors:** Which behaviors are causing the most problems and are most concerning to the patient and family?
- **Setting:** Where and when do the concerning behaviors occur?
- **Scary:** Are there adverse elements in the child's history or present situation (e.g., psychological maltreatment, neglect, physical or sexual abuse, domestic violence, divorce, homelessness, or parental substance abuse)?
- **Screenings/Services:** Based on the patient's longitudinal medical record, have they received prior screenings, treatments, or specialty services?

Harrison J, Wasserman K, Steinberg J, Platt R, et al: The Five S's: a communication tool for child psychiatric access projects. *Current Problems in Pediatric and Adolescent Health Care* 2016; doi 10.1016/j.ccpeds.2016.11.006. From Johns Hopkins University School of Medicine, Baltimore, MD; and other institutions. **Funded by the Maryland Department of Health and Mental Hygiene. The authors did not include disclosure of potential conflicts of interest.**

Deutetrabenazine for Tics

In a phase I pilot study, deutetrabenazine (SD-809), a modified form of tetrabenazine, reduced tic severity in adolescents with Tourette's disorder.

Background: Tetrabenazine, a potential treatment for a variety of hyperkinetic movement disorders, works by depleting dopamine presynaptically. Although generally effective, it is associated with frequent and often intolerable adverse effects including somnolence, nausea, depression, insomnia, akathisia, and parkinsonism. Its active metabolites have short half-lives, requiring dosing ≥ 3 times a day. Deutetrabenazine provides a slower and more consistent metabolism, leading to a more benign side-effect profile and less frequent dosing. The starting dose is about half that of tetrabenazine.

Methods: This pilot study was carried out in 23 adolescents, aged 12–18 years, with Tourette's disorder and motor and/or vocal tics of at least moderate severity. Following blinded genotyping for CYP2D6, which metabolizes the drug, participants received open-label

deutetrabenazine in a 6-week titration period, followed by 2 weeks on the stable final dosage. Deutetrabenazine was started at 6 mg/day, and was increased weekly by 6 mg, to a maximum of 36 mg/day. The primary outcome measure was the Yale Global Tic Severity Scale (YGTSS).

Results: The sample included no poor metabolizers and 3 ultra-rapid metabolizers, based on genotyping. A total of 18 patients were taking concomitant medications at baseline, including stimulants and antidepressants. At study end, 14 patients were taking the maximum daily deutetrabenazine dosage of 36 mg/day. This group included the 3 ultra-rapid metabolizers, which suggests this patient group may require a higher dose. Of the 23 patients enrolled, 3 did not complete the study, but none withdrew because of a treatment-related adverse event.

The mean YGTSS total tic score was 32 at baseline and was reduced to 21 after 8 weeks of treatment (a 37.6% decrease; $p < 0.0001$). More than 60% of patients met criteria for clinically meaningful change ($\geq 25\%$ decrease in tic severity). Participants had statistically significant mean reductions in subscores for both motor and vocal tics (37% and 35%, respectively). Average YGTSS scores increased slightly in the week after the study drug was withdrawn. Secondary study outcomes also supported the efficacy of deutetrabenazine. A total of 86% of patients had a ≥ 1 -point improvement in the Tourette Syndrome Clinical Global Impression (TS-CGI) scale. Average scores decreased from the moderate-to-severe range to the mild-to-moderate range.

Adverse events during treatment were mild to moderate in severity. The most frequent were fatigue and headache, each affecting 4 patients. Smaller numbers experienced irritability, somnolence, hyperhidrosis, diarrhea, and nasopharyngitis. One patient with a history of fluctuating mood had mild suicidal ideation, which resolved during continued treatment.

Discussion: Currently, haloperidol, pimozide, and aripiprazole are the only FDA-approved drugs for the treatment of Tourette's disorder and their use is limited by frequent adverse effects including drowsiness, weight gain, and metabolic syndrome, as well as the potential to cause tardive dyskinesia. While the results of this study support the safety and efficacy of deutetrabenazine, they must be replicated in a stronger study. A larger double-blind, placebo-controlled trial with a longer duration is currently being planned.

Jankovic J, Jimenez-Shahed J, Budman C, Coffey B, et al: Deutetrabenazine in tics associated with Tourette syndrome. *Tremor and Other Hyperkinetic Movements* 2016; doi 10.7916/D8M32W3H. From Baylor College of Medicine, Houston, TX; and other institutions including Auspex, a subsidiary of Teva Pharmaceutical Industries, La Jolla, CA. **Funded by Auspex. All study authors declared financial relationships with commercial sources including Auspex/Teva.**

Common Drug Trade Names: aripiprazole—*Abilify*; haloperidol—*Haldol*; pimozide—*Orap*; tetrabenazine—*Xenazine*

Reference Guide

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 are posted at www.alertpubs.com.

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Nicotine Abuse in Adolescents

The rapidly developing brains of children and adolescents are particularly susceptible to the addictive effects of nicotine, according to a technical report from the American Academy of Pediatrics (AAP).

The traditional model explaining nicotine addiction includes many behavioral, social, environmental, and psychological contributors beyond nicotine itself. A newer model, the sensitization-homeostasis model, has been proposed to explain the development of addiction in adolescents. In this age group, even infrequent smoking, such as once a month, is enough to elevate risk of dependence. Early symptoms of dependence, such as wanting or craving a cigarette, can occur even after the first cigarette. This early urge to have a cigarette drives the adolescent to increase the frequency of smoking, further increasing the risk of dependence. In a predictable sequence, neurophysiological dependence can lead to tolerance and neuroadaptation, which explains why some adolescents report the need for nicotine to function normally.

Particularly concerning is the problem of smoking cessation in adolescents, who are more likely than adults to have difficulty quitting. U.S. Public Health Service guidelines recommend offering pharmacotherapy for all adults who smoke. The currently approved products include over-the-counter nicotine gum and lozenges (both short-acting) and long-acting nicotine patches. Prescription medications include nicotine oral inhalers and nasal sprays, bupropion, and varenicline. A 2015 AAP policy statement recommends consideration of pharmacotherapy in moderately-to-severely nicotine-dependent adolescents, despite problems with adherence, a high relapse rate, and concerns that nicotine (and thus nicotine replacement) can change the neurodevelopmental trajectory. Recent research suggests e-cigarettes may encourage rather than discourage cigarette smoking in adolescents. Anti-addiction vaccines are a promising approach in development, but they are far from clinical use.

Most of the research on tobacco-dependence treatment in adolescents has focused on behavioral interventions. These are most effective in patients with mild dependence but are of some

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benefit in those with severe dependence. Data are limited and do not support any one behavioral approach. The U.S. Public Health Service recommends cognitive-behavioral, motivational, and social-influence strategies.

Siqueira L and AAP Committee on Substance Use and Prevention: Nicotine and tobacco as substances of abuse in children and adolescents. *Pediatrics* 2017;doi 10.1542.peds.2016-3436. From the American Academy of Pediatrics. **The report was produced with no external funding. The author declared no relevant financial relationships.**

Common Drug Trade Names: bupropion—*Wellbutrin*; varenicline—*Chantix*

Antecedents of Depression Onset in At-Risk Children

In children at high familial risk of depression, the onset of clinical depression is predicted by irritability and fear or anxiety, as well as familial and social factors, according to an analysis of longitudinal data from the U.K. that modeled the effects of multiple antecedents simultaneously.¹

Methods: Study participants were families recruited mainly from U.K. general practices and that included a parent with history of ≥ 2 episodes of recurrent depression. To reduce the likelihood that the child had already experienced depression, the study included each family's youngest child between the ages of 9 and 17 years. Parents and children were assessed on 3 occasions: at baseline, after an average of 16 months, and then after an additional 12 months. The primary outcome, new onset of major depressive disorder in the child, was assessed using the Child and Adolescent Psychiatric Assessment. The data were analyzed with structural equation modeling, which allowed simultaneous evaluation of all measured risk factors and all hypothesized risk paths. The model included indexes of the degree of familial risk and of social adversity, the latter consisting of stressful life events in the last 12 months and low family income. The analysis also included 4 dimensional clinical antecedent variables: low mood, fear/anxiety, irritability, and disruptive behavior.

Results: The study sample consisted of 279 families with complete data, including diagnostic information on the child. New-onset depression occurred in 20 offspring—6 boys and 14 girls—at a mean age of 14 years. Of the 4 clinical antecedents, irritability and fear/anxiety were significantly associated with depression onset ($p=0.03$ and $p<0.001$, respectively). In contrast, after allowing for other factors in the model, low mood and disruptive behavior did not predict depression onset. The path from fear/anxiety to depression was significantly stronger than the path from irritability. These 2 factors had a low but significant association with each other, which suggests they do not often occur together.

Indexes of familial risk were associated with depression onset directly, but not with the clinical antecedents. Economic disadvantage and stressful life events had significant effects on both depression onset and the clinical antecedents, but none of their effect on depression occurred via the clinical antecedents.

Discussion: These observations suggest that efforts to prevent depression in children and adolescents should address not only clinical phenomena in the child, but also risk factors occurring in a broader context. Family-based programs should treat depression in the parent, because it is associated with social adversity and may interfere with preventive efforts in the child. Prevention programs may need to target social phenomena to overcome the effects of poverty and psychosocial adversity.

Editorial.² This research highlights the contrast between selective and universal depression prevention efforts. Studies in the U.S. show that selective programs, focused on high-risk

Predictors of Depression in At-Risk Adolescents

Clinical Antecedents

Irritability

Fear/Anxiety

Familial Risk Factors

Severity of parental depression

Additional family history

Psychosocial adversity

Economic disadvantage

individuals, outperform universal prevention programs. However, a small effect size can translate to large effects at the population level. In the U.S., antecedents of depression may interact differently for large subgroups of children affected by environmental factors such as interpersonal violence and inadequate health care access.

¹Rice F, Sellers R, Hammerton G, Eyre O, et al: Antecedents of new-onset major depressive disorder in children and adolescents at high familial risk. *JAMA Psychiatry* 2017;74 (February):153–160. From Cardiff University, Wales; and other institutions. **Funded by the Sir Jules Thorn Charitable Trust; and other sources. The authors declared no competing interests.**

²Glowinski A, Rosen M: Prevention targets for child and adolescent depression [editorial]. *JAMA Psychiatry* 2017;74 (February):160–161. From Washington University School of Medicine, St. Louis, MO. **The authors declared no financial relationships with commercial sources.**

New Methylphenidate Formulations

New formulations of methylphenidate, either recently FDA approved or in development, were designed to improve treatment adherence and tolerability and to prevent misuse. The new formulations can overcome children's difficulty in swallowing capsules or tablets, reduce the number of administrations per day, ensure therapeutic effects throughout the day, and prevent the ill effects of dosage peaks. Although the new formulations appear to be effective and well tolerated, existing research merely sets the groundwork for future detailed studies of these agents.

A comprehensive literature review was undertaken to examine clinical and pharmacokinetic studies of both methylphenidate formulations in development and forms that have been approved in the past 5 years. A total of 6 new formulations were identified. (See table.)

New Methylphenidate Formulations			
Formulation	Trade Name	Approval Status	Improvement
Methylphenidate XR oral suspension (MEROS)	<i>Quillivant</i>	FDA approved 2012	Liquid suspension
Methylphenidate ER chewable tablets	<i>QuilliChew ER</i>	FDA approved 2015	Chewable tablet
Methylphenidate hydrochloride XR capsules	<i>Aptensio XR</i>	FDA approved 2015	Bioequivalent capsule and sprinkles
Methylphenidate XR orally-disintegrating tablets (ODT)	<i>Contempla</i>	FDA approval pending	Orally disintegrating tablet
Methylphenidate modified-release (HLD-200)	<i>Bejorna</i>	FDA approval pending	Delayed-release and XR capsules
Methylphenidate SR once-daily tamper resistant	<i>ORADUR technology</i>	In development (phase III)	Converts short-acting oral capsule dosages to sustained-release products

MEROS is the first extended-release oral suspension of methylphenidate. It contains 20% immediate-release and 80% extended-release methylphenidate. The pharmacokinetics are linear and proportional to dose. Clinical effects have onset 45 minutes after administration and last through 12 hours. Weight-based dosing is not necessary. Tolerability is consistent with known effects of methylphenidate.

Flavored methylphenidate extended-release chewable tablets contain 30% immediate-release and 70% extended-release methylphenidate. There are no known peer-reviewed, published studies of its efficacy.

Methylphenidate hydrochloride extended-release capsules contain 40% immediate-release and 60% extended-release methylphenidate, the latter in controlled-release layers. Pharmacokinetic profiles are highly variable in children and adolescents, which suggests an individualized, titration-based dosing regimen. There have been reports of severe drug-related adverse events: aggression and mood swings.

For the 2 formulations pending approval, less pharmacokinetic and clinical information is available. These formulations are an orally disintegrating methylphenidate extended-release tablet and a modified-release formulation, called HLD-200, with a novel delivery platform that allows the drug to be given at nighttime, followed by symptom control immediately upon waking.

ORADUR, now in phase III clinical trials, is a new technology that provides sustained delivery, reducing the potential for abuse by unapproved methods of administration, such as snorting or injecting. ORADUR would thwart patients' crushing, extracting, or otherwise tampering with the drug, since the sustained-release technology would prevent achieving a "high."

Cortese S, D'Acunto G, Konofal E, Masi G, et al: New formulations of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: pharmacokinetics, efficacy, and tolerability. *CNS Drugs* 2017; doi 10.1007/s40263-017-0409-0. From the University of Southampton, U.K.; and other institutions including NLS-Pharma, Switzerland. **This review was conducted without funding. The authors declared no relevant competing interests.**

Common Drug Trade Names: methylphenidate XR oral suspension—*Quillivant XR*; methylphenidate XR chewable tablets—*QuilliChew ER*; methylphenidate hydrochloride XR tablets—*Aptensio XR*; methylphenidate XR ODT—*Cotempla XR ODT*; HLD-200 (methylphenidate modified-release)—*Bejorna*

Internet CBT for OCD in Adolescents

Therapist-guided, parent-supported, internet-delivered cognitive behavioral therapy (ICBT) significantly improved symptoms of obsessive-compulsive disorder in adolescents in a randomized trial.¹ Effects were more modest than expected, but the intervention was conducted with <20 minutes per week of therapist time.

Methods: The 12-week ICBT program was tested in adolescents, aged 12–17 years, who were screened by telephone interview and assessed in person with a full diagnostic interview. Enrollment criteria included a primary diagnosis of OCD, meeting a severity threshold of ≥ 16 on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), and daily access to the internet. Patients were randomly assigned to immediate treatment or to a waiting list of equivalent duration. ICBT consisted of 12 chapters containing text, audiovisuals, and exercises for patients to do on their own or with parents. The amount of parent involvement was tailored to the adolescent's developmental needs. The primary outcome measure was the CY-BOCS, assessed immediately post-treatment and again after 3 months. Patients assigned to the waiting list were offered ICBT after 12 weeks.

Results: The trial enrolled 67 patients (46% girls) with a mean age of 15 years. About 20% of the adolescents were taking medications (either SSRIs or stimulants, which were required to be unchanged for ≥ 6 weeks before study entry) during ICBT. Of 33 patients initially assigned to ICBT, 1 withdrew from treatment prematurely. Of the 34 patients assigned to the wait-list control, 28 chose to start ICBT at 12 weeks.

Mean baseline CY-BOCS scores were 23 and 22 in the ICBT and waitlist groups, respectively. At the post-treatment assessment, patients who received ICBT had significantly lower CY-BOCS total scores than controls (17 vs 21; $p < 0.001$; between-group effect size,* 0.69). The ICBT group continued to improve during the 3 months until follow-up when the mean Y-BOCS

score was 14 (within-group effect sizes, 1.09 from pre- to post-treatment and 1.68 from pre-treatment to 3-month follow-up). One-fourth of the ICBT group received additional new treatments during follow-up, but excluding these patients from the analysis did not substantially affect outcomes. A total of 9 patients in the ICBT group (27%) were classified as responders (i.e., $\geq 35\%$ decrease in CY-BOCS score plus a Clinical Global Impression–Improvement* score of ≤ 2) post-treatment, and 10 patients (32%) met these criteria at 3 months. Remission (i.e., CY-BOCS score of ≤ 12 plus a Clinical Global Impression–Severity* score of ≤ 2) occurred in 5 and 8 patients (15% and 26%) at post-treatment and 3 months, respectively. No patient in the wait-list group achieved response or remission. After crossover to active treatment, the former control group also benefitted from treatment: 10 experienced response and 7 achieved remission at post-treatment, with further gains made after 3 months.

Patients completed a mean of 9 of the 12 chapters of the program. The average clinician time per patient, per week, was 17.5 minutes, spent mainly in reading patient exercises, written feedback, and telephone calls. This is about one-third to one-fourth the time therapists would have spent in standard face-to-face CBT. About half of the adolescents were satisfied with the program's format, and half said they would have preferred to meet with a therapist occasionally.

According to an accompanying editorial,² therapist-assisted ICBT could extend the reach of therapy in several ways: as part of a stepped-care model, to bridge the gap before therapy in young people who have been placed on a long waiting list, in sessions alternating with in-person CBT, or in patients who cannot tolerate clinic visits or who live too far away.

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

¹Lenhard F, Andersson E, Mataix-Cols D, Ruck C, et al: Therapist-guided, internet-delivered cognitive-behavioral therapy for adolescents with obsessive-compulsive disorder: a randomized controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 2017;56 (January):10–19. From the Karolinska Institutet; and Stockholm Health Care Services, Sweden. **Funded by the Stockholm County Council; and other sources. The authors declared no competing interests.**

²Myers K, Vander Stoep A: i-therapy: asynchronous telehealth expands access to mental health care and challenges tenets of the therapeutic process [editorial]. *Journal of the American Academy of Child and Adolescent Psychiatry* 2017;56 (January):5–7. From the University of Washington School of Medicine, Seattle; and other institutions. **The authors declared no competing interests.**

*See Reference Guide.

Marine Oil Extract for ADHD Symptoms

In a manufacturer-sponsored, placebo-controlled trial, a fish oil extract did not improve hyperactivity, inattention, or impulsivity in children with ADHD. However, the supplements did have positive effects in a subset of children with subclinical hyperactivity or impulsiveness, but not both.

Background: Results of previous clinical trials suggest long-chain polyunsaturated fatty acid supplements are beneficial in ADHD, and they have even been suggested as an alternative to stimulants. PCSO-524 is a standardized lipid extract of the New Zealand green-lipped mussel and contains a unique combination of free fatty acids, sterol esters, polar lipids, and carotenoids. It is available over the counter as *Lyprinol* and *OmegaXL*. In children with ADHD, the supplement may have antiinflammatory and antiallergic effects, which could theoretically lead to improvement in ADHD symptoms.

Methods: PCSO-524 was evaluated in children, aged 6–14 years, with elevated levels of hyperactivity, inattention, or both, according to scores on the DSM-IV ADHD Rating Scale. Participants were randomly assigned to receive PCSO-524 or placebo (3 or 4 capsules daily, based on weight) for 14 weeks. The primary study outcome measure was the Conners Parent Rating Scale (CPRS).

Results: The final analysis included 112 participants, of whom 50 had a DSM diagnosis of ADHD and 35 were taking a stimulant or atomoxetine (*Strattera*). All statistical analyses were adjusted for ADHD and medication status. After 14 weeks of treatment, control subjects and patients who received PCSO-524 did not differ overall on average CPRS scores. An exploratory subgroup analysis showed that children with the most severe symptoms—those with combined high hyperactivity and high impulsivity—did not improve with treatment, but those with less severe symptoms did. This group included 43 children with high hyperactivity or high impulsivity, but not both. In this group, those who received PCSO-524 showed significant improvement in CPRS scores for hyperactivity ($p=0.04$), learning abilities ($p=0.05$), and behavior at home ($p=0.02$), as well as improvement on DSM scores of inattention ($p=0.02$) and hyperactivity ($p=0.04$), compared with placebo-treated children with the same symptom profile. Further analysis indicated that children with high baseline inattention scores showed improvement in parental ratings of executive function, aggression, conduct, and oppositional defiance, with effect sizes in the medium-to-large range. There were no improvements in any of these behavioral measures for children showing high hyperactivity at baseline. PCSO-524 was associated with transient improvement in some secondary outcome measures of cognitive function.

Discussion: Based on the results of this study, large-scale clinical trials of PCSO-524 supplementation appear to be warranted in young patients with subclinical ADHD symptoms.

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

Kean J, Sarris J, Scholey A, Silberstein R, et al: Reduced inattention and hyperactivity and improved cognition after marine oil extract (PCSO-524®) supplementation in children and adolescents with clinical and subclinical symptoms of attention-deficit hyperactivity disorder (ADHD): a randomised, double-blind, placebo-controlled trial. *Psychopharmacology* 2017;234 (February):403–420. From Swinburne University of Technology, Hawthorn; and the University of Melbourne, Australia. **Funded by Pharmed Pty Ltd. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

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.

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.

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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Comparative Efficacy of ADHD Treatments

According to the results of a manufacturer-sponsored network meta-analysis,* lisdexamfetamine appears to be the most effective among agents approved in the U.K. for treatment of ADHD in children and adolescents, while immediate-release (IR) methylphenidate appears to have the best tolerability.

Methods: A comprehensive literature search was undertaken to identify randomized controlled trials of dextroamphetamine, atomoxetine, IR clonidine, IR or extended release (ER) guanfacine, lisdexamfetamine, or IR or ER/OROS methylphenidate for treatment of ADHD in patients aged 6–17 years. Studies were included in the network meta-analysis if treatment duration was ≤16 weeks and the study drug could be connected to either of the nonstimulants by a chain of common comparators. Efficacy outcomes, which differed by study, included change in total ADHD Rating Scale-IV (ADHD-RS-IV) total score and Clinical Global Impression–Improvement (CGI-I) response, defined as a rating of much improved or very much improved. Safety endpoints included discontinuation for any reason and for adverse effects.

Results: A total of 36 studies met inclusion criteria; of these, 20 evaluated ADHD-RS-IV change, 14 evaluated CGI-I response, 31 reported all-cause discontinuation, and 32 reported discontinuation due to adverse effects. Study durations ranged from 3 to 16 weeks, and treatment arms included 16–222 subjects. Mean baseline ADHD-RS-IV scores, available from 22 studies, ranged from 31.5 to 43.5. Data was insufficient to include dextroamphetamine, clonidine, and IR guanfacine in the network analysis.

Efficacy of lisdexamfetamine was superior to all other treatments when measured using either ADHD-RS-IV or CGI-I change. (See table, next page.) The calculated probability of lisdexamfetamine being the most effective pharmacotherapy was 99.96% for ADHD-RS-IV change and 96.21 for CGI-I response. When only nonstimulants were considered, ER guanfacine was superior to atomoxetine for both efficacy outcomes. Among the agents, IR methylphenidate was the best tolerated, with the lowest rates of both all-cause discontinuation and adverse

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effect-related discontinuation. However, sample sizes for safety outcomes were small and statistical uncertainty was high. Of the nonstimulants, atomoxetine was less likely than guanfacine to be discontinued. (See table.)

Efficacy Outcomes of ADHD Treatments		
Efficacy	ADHD-RS-IV Score: Decrease from Baseline Relative to Placebo	Odds Ratio* for CGI-I Response vs Placebo
Lisdexamfetamine	14.98	8.43
ER Methylphenidate	9.33	4.27
ER Guanfacine	8.68	3.34
Atomoxetine	6.88	2.69
IR Methylphenidate	Not evaluated	2.22
Safety	Relative Risk* for All-Cause Discontinuation	Relative Risk for Adverse Effect Discontinuation
IR Methylphenidate	0.44	1.20
ER Methylphenidate	0.52	1.38
Lisdexamfetamine	0.66	3.11
ER Guanfacine	0.87	4.49
Atomoxetine	0.88	2.39

Discussion: While these results suggest lisdexamfetamine is the most effective agent and IR methylphenidate the best tolerated, the clinical implications are limited because no risk–benefit assessment was conducted in the study. This type of comparison would be useful to better inform clinical practice.

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

Joseph A, Ayyagari R, Xie M, Cai S, et al: Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison. *European Child and Adolescent Psychiatry* 2016; doi 10.1007/s00787-017-0962-6. From Shire, Switzerland and Wayne, PA; and other institutions. Funded by Shire. All study authors disclosed financial relationships with commercial sources.

Common Drug Trade Names: atomoxetine—*Strattera*; clonidine—*Catapres*; dexamphetamine—*Dexedrine*; ER guanfacine—*Intuniv*; IR guanfacine—*Tenex*; lisdexamfetamine—*Vyvanse*; ER/OROS methylphenidate—*Concerta*; IR methylphenidate—*Ritalin*

*See Reference Guide.

CBT for Selective Mutism

In a pilot study, the brief family-based cognitive-behavioral intervention Social Communication Anxiety Treatment (S-CAT) improved children's selective mutism and the accompanying anxiety and social withdrawal.

Methods: Study families (n=40) had contacted a specialty practice for selective mutism to take advantage of a grant-funded, free-of-charge treatment. All children (mean age, 7 years) had a prior diagnosis of selective mutism, which was confirmed by treating clinicians based on DSM-IV or DSM-5 criteria and scores on several standardized symptom questionnaires. The primary outcome measure was the Selective Mutism Questionnaire (SMQ), a 17-item parent questionnaire that rates the child's frequency of speaking, with subscales for at school, at home, and in public or social situations. S-CAT was delivered in 3 sessions, once every 3 weeks, with guided homework in between. Important elements of the treatment include the therapist's "nonchalant" technique, with low pressure on the child to speak; reducing parents'

enabling behaviors and children's avoidance behaviors; and using behavioral and cognitive strategies to help children communicate in increasingly challenging situations. Children were evaluated before each therapy session and at the final follow-up at week 15 (6 weeks after the last office session). A complete description of S-CAT therapy is available at www.selectivemutismcenter.org/aboutus/SelectiveMutism.Treatment.ShiponBlum.

Results: The 33 children who completed study treatment showed a significant increase in speech after the first 3 weeks and continued to improve throughout the study and follow-up. At the 15-week follow-up, children demonstrated statistically significant improvement in speaking frequency, as measured with the SMQ total score and the family, school, and public/social subscales ($p < 0.001$ for linear trend for each outcome). Among individual items on the SMQ, the largest gains were in social situations outside of school, such as speaking with store clerks or unknown children. Even at home, where children were already speaking, the frequency of speech with family friends and babysitters doubled. Larger gains were associated with family compliance and with lower initial symptom severity. Children also showed reduced parent-rated anxiety and withdrawal, according to the Child Behavior Checklist.

Discussion: There have been many published studies of selective mutism treatment, but most are single-case reports. The few more rigorous studies have suggested cognitive-behavioral approaches are promising. Among these, S-CAT may be particularly effective because activities are guided by the child's comfort level, the therapist minimizes expectations and pressure to speak, parents are heavily involved, and motivation is an important element of treatment.

Klein E, Armstrong S, Skira K, Gordon J: Social Communication Anxiety Treatment (S-CAT) for children and families with selective mutism: a pilot study. *Clinical Child Psychology and Psychiatry* 2017;22 (January):90–108. From La Salle University, Philadelphia; and the Selective Mutism Research Institute, Jenkintown, PA. **Funded by the Selective Mutism Research Institute. The authors did not include disclosure of potential conflicts of interest.**

Cognitive Control Deficits and Suicide Risk

In a group of hospitalized adolescents, deficits in cognitive control were associated with a history of suicide attempts. These deficits may be a useful addition to suicide risk assessment because they do not depend on potentially unreliable patient report.

Background: Cognitive control refers to the ability to adapt attention, thoughts, or behavior to facilitate an internal goal. In the Suicide Stroop Task (SST), used in this study to measure cognitive deficits, subjects are shown words and asked to name the ink color. The content of each word may be either suicide-related or emotionally positive, negative, or neutral. Difference in reaction times between individual word categories indicates interference, and increased interference reflects cognitive control deficits. Adults with suicidality have been shown to have increased interference with suicide-related words, but this appears to be the first study of cognitive control using the SST in adolescents with suicidality.

Methods: Adolescents who reported suicidal ideation on ≥ 1 day during the previous week were recruited within 48 hours of admission to a short-term inpatient treatment program. A total of 98 patients (aged 13–18 years; 71 girls) were eligible and agreed to participate in the study. The group included 60 adolescents with only suicidal ideation and 38 with ≥ 1 lifetime suicide attempt, of whom 26 had multiple attempts. Each participant had 48 trials of the SST, with an equal number of randomly-ordered words that were positive, negative, neutral, and suicide-related. Only correct responses (i.e., correct color identification) were included in the analysis.

Results: Total reaction times and number of errors did not differ significantly across groups. In addition, the groups did not differ in terms of negative or neutral interference. However, patterns did emerge in terms of suicidal and positive interference.

Suicidal term-related interference. In patients who had attempted suicide, interference from suicide-related terms was significantly greater than in those with suicidal ideation ($p=0.044$; effect size,* 0.41). Multiple attempters had even greater interference than those with only ideation ($p=0.004$; effect size, 0.64). No significant differences were found between single and multiple attempters or between single attempters and ideators.

Positive term-related interference. Suicide attempters also had greater interference from positive words than did those with suicidal ideation ($p=0.01$; effect size, 0.53). Again, effects were larger for adolescents with multiple attempts than ideators ($p<0.001$; effect size, 0.79) and for multiple versus single attempters ($p=0.03$; effect size, 0.76). Only interference from positive emotional stimuli was associated with the recency of a suicide attempt.

Discussion: One-third of adolescents with suicidal ideation transition to a suicide attempt. This study suggests interference from emotional stimuli, regardless of positive or negative valence, may be a marker of risk, particularly for multiple attempters. The results suggest that following negative life events, deficits in cognitive control may hinder suicidal adolescents from directing their attention away from hopelessness and other negative affective states. Interventions that provide tools to manage their emotions, such as distraction or mindfulness, may be especially useful in preventing suicide.

Stewart J, Glenn C, Esposito E, Cha C, et al: Cognitive control deficits differentiate adolescent suicide ideators from attempters. *Journal of Clinical Psychiatry* 2016; doi 10.4088/JCP.16m10647. From Harvard Medical School, Cambridge, MA; and other institutions. **Funded by the NIMH; and other sources. The authors declared no competing interests.**

*See Reference Guide.

Circadian Rhythm Disturbance and Psychosis

In a longitudinal study of adolescents and young adults at high risk of psychosis, circadian rhythm disturbances were predictive of worsening symptoms.

Background: The sleep-wake cycle is comprised of 2 interacting processes: homeostatic sleep and the circadian pacemaker. Previous research suggests disrupted sleep-wake cycles increase the severity of psychosis and predict relapse of psychotic episodes, but less is known about the effects of circadian disruptions.

Methods: Study participants, aged 12–21 years, were enrolled in an ongoing study of clinical high-risk (CHR) youth who had either attenuated positive psychosis symptoms of moderate severity or global functioning declines plus a family history of psychosis or schizotypal personality disorder. In the 34 CHR subjects and 32 healthy controls, symptoms were assessed at study entry with the Structured Interview for Prodromal Symptoms, the Structured Clinical Interview for DSM-IV, and the Global Assessment of Functioning. Circadian rhythms were measured at baseline using a wrist actigraph worn continuously for 5 days. Clinical assessments were repeated 1 year after baseline.

Results: At study entry, 3 patients in the CHR group were taking antipsychotic medication. At follow-up, 4 patients were taking antipsychotics, 2 of whom had continued to receive the medication from baseline.

At baseline, after adjusting for age, gender, and depression symptoms, CHR subjects had significantly greater rhythm fragmentation ($p=0.04$) and later onset of nocturnal rest ($p=0.04$) than controls. Baseline severity of positive symptoms was associated with greater

rhythm fragmentation, lower diurnal activity, and increased intra-daily variability in rest-activity fragmentation (all $p < 0.05$). Baseline negative symptoms were significantly correlated with decreased activity during the most and least active periods of the day ($p < 0.05$).

Multiple measures of circadian variability at baseline were associated with longitudinal worsening of symptoms and function among CHR adolescents. After adjustment for baseline symptoms, age, gender, and depression, severity of positive symptoms at 1 year was associated with reduced diurnal activity, reduced difference between day and night activity, reduced inter-daily stability (synchronization of circadian rhythm with light-dark cycle), and increased intra-daily variability (all $p < 0.05$). Decreased diurnal activity was associated with worsening of negative symptoms ($p < 0.05$). Worsening of psychosocial functioning at 1 year was predicted by reduced diurnal activity, reduced relative day/night amplitude, increased rhythm fragmentation, greater intra-daily variability, and later onset of the most active period of the day.

Discussion: The present study indicates circadian rhythm disturbance may be an important modifiable factor in the conversion to psychosis in high-risk youth. Interventions that can alter daily rhythm synchronizers include increasing the regularity of social routines such as bedtime, wake time, and meals; improving light-dark synchronization by increasing daytime light exposure and reducing nighttime exposure to light and electronic devices; and increasing daytime physical activity.

Lunsford-Avery J, Goncalves B, Brietzke E, Bressan R, et al: Adolescents at clinical-high risk for psychosis: circadian rhythm disturbances predict worsened prognosis at 1-year follow-up. *Schizophrenia Research* 2017; doi 10.1016/j.schres.2017.01.051. From Duke University Medical Center, Durham, NC; and other institutions. **Funded by the NIH. One study author disclosed a financial relationship with a commercial source; the remaining 6 authors declared no competing interests.**

Citalopram and Emotional Regulation

In children and adolescents with anxiety disorders, treatment with citalopram (*Celexa*) was associated with improvement in reappraisal ability—the ability to change an emotional response by reinterpreting the meaning of the emotional stimulus—a key mechanism of emotional regulation.

Methods: Participants in this open-label observational study were 50 children and adolescents, aged 10–17 years, seeking treatment at an anxiety disorder clinic within a tertiary pediatric medical center. A total of 35 patients immediately began treatment with citalopram, and the remaining 15 had refused the medication and were placed on the clinic's waiting list for cognitive behavioral therapy. Two computerized tests of emotional reactivity and regulation were developed for the study. The Reactivity and Regulation-Situations (REAR-S) test exposes the child to ambiguous situations taken from daily life and asks the child to rate their initial emotional reaction, reappraise the situation, and then rate the efficacy of the reappraisal. The REAR-S tests 2 aspects of negative emotional reactivity—frequency and intensity—and 3 aspects of reappraisal—uninstructed, cued, and self-efficacy. The Reactivity and Regulation-Images (REAR-I) test is similar but exposes the participant to images with threatening content. This test assesses the intensity of negative emotional reactivity, cued reappraisal ability, and reappraisal efficacy. Patients completed the computerized tasks and questionnaire-based symptom assessments at enrollment and after 8 weeks.

Results: Compared with the wait-list group, patients who received citalopram showed larger improvements in illness severity and parent ratings of anxiety after 8 weeks. Remission—a Clinical Global Impression–Severity* score of ≤ 2 —was documented after 8 weeks in 16 patients who received citalopram and in 2 wait-listed patients (44% vs 13%, respectively; $p = 0.02$).

Emotional reactivity scores decreased to a similar extent in both treatment groups. However, compared with the wait-list group, patients who received citalopram had greater improvement in cued reappraisal ability on the REAR-I. This group also showed improvement in reappraisal ability on the REAR-I, but not the REAR-S. None of the reappraisal parameters improved in the wait-list group, and these patients had a decrease in reappraisal efficacy after 8 weeks ($p < 0.05$).

In medicated patients, improvement in reappraisal ability was modestly but significantly correlated with overall clinical improvement (correlation coefficient, -0.03 ; $p < 0.04$) and a decrease in anxiety (correlation coefficient, -0.038 ; $p < 0.02$). In the combined group of patients, decreases in the intensity of emotional response on the REAR-S were correlated with decreases in anxiety (correlation coefficient, 0.44 ; $p < 0.001$) and with overall clinical improvement (correlation coefficient, 0.27 ; $p < 0.05$).

Discussion: The primary finding of this study, although preliminary, was a greater increase in cued reappraisal ability in patients taking medication, which suggests SSRI therapy may improve patients' ability to provide alternative explanations of threatening events. Medication-associated changes in reappraisal were more sensitive on the REAR-I task than the REAR-S task. This could potentially be explained by the difference in visual (REAR-I) and situational (REAR-S) tasks, which activate differing neural pathways. Clinically, the results suggest a distinction between negative emotional hyperreactivity, which is less directly controllable, and emotional regulation, which can be controlled and potentially taught.

Carthy T, Benaroya-Milshtein N, Valevski A, Apter A: Emotional reactivity and regulation following citalopram therapy in children and adolescents with anxiety disorders. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (February):43–51. From Schneider Children's Medical Center of Israel, Petah Tikva; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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.

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 indicated 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.

Network Meta-Analysis: A statistical 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 or more 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.

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.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) 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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Acute Antipsychotic Treatments Compared

Most available antipsychotics are similarly effective for acute treatment of early-onset schizophrenia, according to a network meta-analysis. However, adverse-effect profiles differ considerably. Based on the risk-benefit profiles, aripiprazole and quetiapine can be recommended as first-line therapy.

Background: Previously, standard pairwise meta-analyses suggested equivalent but minimal efficacy of different agents in early-onset schizophrenia; the network meta-analysis is a way to maximize the sparse information from existing clinical trials.

Methods: The analysis was based on all available trials (excluding trials from China due to validity concerns) of an antipsychotic compared with a placebo control or an active comparator in patients aged ≤ 19 years. Patients fulfilled DSM-5 or ICD-10 criteria for schizophrenia spectrum disorders, excluding affective psychoses. Studies in patients with refractory disease were excluded. Pharmaceutical companies were asked to provide unpublished data. The analysis compared the major efficacy outcomes of mean change from baseline on total and positive symptoms on the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale, and a number of negative outcomes including body weight, extrapyramidal symptoms, and treatment discontinuation.

Results: The network meta-analysis included 12 studies with a total of 2158 patients. There were 8 placebo-controlled trials and 4 with 2 or 3 active comparators. Patients had an average age of 15 years (range, 8–19 years), and 61% were male. Treatment arms included aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, and molindone. Patients received treatment for 6–12 weeks. The studies' risk of bias was generally low.

Most agents had comparable effects on PANSS total, positive, and negative symptoms. The exception was ziprasidone, which showed inferiority on PANSS total symptoms compared with molindone, olanzapine, paliperidone, quetiapine, and risperidone. Ziprasidone was also less effective in terms of PANSS negative symptoms than molindone, olanzapine, and

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risperidone and less effective on Clinical Global Impression (CGI) Improvement scores than olanzapine and risperidone. Effects on CGI-Severity scores did not differ among treatments. All antipsychotics except ziprasidone and asenapine were superior to placebo for the PANSS total symptom change.

Among antipsychotic-related harms, olanzapine, quetiapine, and risperidone produced more clinically significant weight gain compared with placebo in significantly larger proportions of patients. All of the agents except asenapine, olanzapine, and quetiapine produced more extrapyramidal effects than placebo. All drugs except asenapine, quetiapine, and ziprasidone produced more akathisia than placebo. Increases in prolactin were greater than placebo for risperidone, paliperidone, and olanzapine; similar to placebo for molindone and quetiapine; and lower than placebo for aripiprazole. Discontinuation of treatment for any reason or for adverse events did not differ from placebo for any antipsychotic.

Discussion: Of the 8 antipsychotics, 6 appear to be unsuited for first-line treatment in this patient population. Aripiprazole and quetiapine had the most favorable balance of efficacy and tolerability, although even these agents had significant adverse effects.

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

Pagsberg A, Tarp S, Glintborg D, Steinstrom A, et al: Acute antipsychotic treatment of children and adolescents with schizophrenia-spectrum disorders: a systematic review and network meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry* 2017;56 (March):191–202. From Mental Health Services, Capital Region of Denmark and the University of Copenhagen, Denmark; and other institutions. **Funded by RADS—the Danish Council for the Use of Expensive Hospital Medicines; and other sources. Three study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

Common Drug Trade Names: aripiprazole—*Abilify*; asenapine—*Saphris*; molindone—*Moban*; olanzapine—*Zyprexa*; paliperidone—*Invega*; quetiapine—*Seroquel*; risperidone—*Risperdal*; ziprasidone—*Geodon*

*See Reference Guide.

Time Perception in ADHD

In a clinical study, unmedicated boys with ADHD demonstrated significant deficits in time perception and processing speed, compared with boys with other psychiatric disorders.

Methods: Study participants were 103 boys, aged 7–16 years, referred for diagnostic assessment to an outpatient clinic of a psychiatric hospital. All were suspected of having ADHD on the basis of parent- or teacher-reported symptoms. Only those who eventually received a psychiatric diagnosis (excluding autism, low IQ, psychosis, PTSD, and some others) were included in the analysis: 50 with ADHD and 53 with other disorders, predominantly anxiety, adjustment, conduct, or learning disorders. During their clinical evaluation for ADHD, all patients completed the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV). In addition, they were asked retrospectively to estimate the amount of time it took them to complete the Matrix Reasoning subtest of the WISC-IV.

Results: Both groups completed the Matrix Reasoning subtest of the WISC-IV in an average of 5.5 minutes. WISC-IV processing-speed scores were significantly lower for the boys with ADHD ($p < 0.001$). The groups did not differ in WISC-IV full-scale IQ, verbal comprehension, perceptual reasoning, or working memory scores.

Time estimation in boys with ADHD had greater systematic error—i.e., they gave significantly higher time estimates than those with other disorders, overestimating the time by an average of 40%, compared with 3% in controls ($p < 0.001$). Accuracy scores, reflecting deviation from the true value in either a positive or negative direction, were nearly twice as high for boys with ADHD as controls ($p = 0.003$). In boys with ADHD, but not those with other disorders, processing speed was negatively correlated with both systematic error and accuracy. Results of

all analyses were similar in subgroups of boys with either the combined or predominantly inattentive ADHD subtype.

Discussion: Deficits in temporal processing are believed to be 1 of several primary causes of ADHD symptoms. Persons with ADHD are believed to have a faster internal pacemaker-accumulator clock. Time estimation for tasks can be measured retrospectively, as in this study, or prospectively, by informing subjects beforehand that they will be asked to estimate time. Both appear to be altered in ADHD. The 2 tasks have different mechanisms—prospective timing takes attention away from the task at hand, while retrospective timing may be based on alterations in pacemaker speed or reference memory. The present study differs from previous research in testing retrospective time estimation for a relatively long task duration of about 5 minutes and by including a control group with disorders that may emulate true ADHD. The present results suggest that assessing retrospective time estimation may be useful in the differential diagnosis of ADHD.

Walg M, Hapfelmeier G, El-Wahsch D, Prior H: The faster internal clock in ADHD is related to lower processing speed: WISC-IV profile analyses and time estimation tasks facilitate the distinction between real ADHD and pseudo-ADHD. *European Child and Adolescent Psychiatry* 2017; doi 10.1007/s00787-017-0971-5. From the Zentrum für seelische Gesundheit des Kindes und Jugendalters, Remscheid, Germany; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

Neuropsychiatric Risks of Adolescent Cannabis Use

Current clinical research indicates that exposure to cannabis in adolescence is associated with poor cognitive and psychiatric outcomes in adulthood, according to a review. It is difficult to know the extent to which cannabis is a cause of these outcomes, since it coexists with an "entire landscape" of other influences. Studies in animals can directly measure the effect of cannabis on the adolescent brain, but the preclinical and clinical research do not always point to the same conclusions.

The expansion of recreational marijuana will likely lead to increased access by adolescents, who now use cannabis more than cigarettes. Adolescents also have legal access to a constant stream of new, synthetic cannabinoids whose introduction outpaces legal regulation and that can have very different effects from cannabis. The data thus far suggest that cannabis is a markedly less harmful recreational drug than alcohol or tobacco when used in adults, but decades of research suggest early-onset cannabis use is associated with negative life outcomes.

Ethical concerns limit research in young subjects to observational rather than experimental designs, which makes it difficult to explore the direction of causation. Genetic studies suggest cannabis use and psychiatric disorders, such as depression and schizophrenia, may share a common liability.

Adolescent-onset cannabis use is associated with cognitive deficits, such as impaired attention, memory, and visual processing, and decreased full-scale and verbal IQ. These cognitive sequelae may be limited to persons who began using cannabis before age 15 or 16 years; they do not appear to affect late-onset adolescent users, and it is not clear whether they improve if cannabis use is discontinued. Despite methodological limitations, research suggests early-onset or frequent marijuana use is also associated with mood and anxiety disorders. Alternative explanations for the association include shared vulnerability and self-medication of emerging emotional symptoms. Evidence of an association with suicidal behavior or ideation is inconsistent. There is a well-documented higher prevalence of early-onset cannabis use in persons with psychosis, and adults with a psychotic disorder and early-onset cannabis use have more frequent relapses, poorer treatment adherence, and increased hospitalization. Early cannabis use is associated with later nicotine dependence and substance use disorders, but again the role of common behavioral and genetic liability is unclear.

Animal models of cannabis exposure can help clarify its effects on the adolescent brain. These experiments suggest adolescent animals are uniquely vulnerable to long-term consequences of cannabis exposure, similar to outcomes seen in humans, including altered later-life cognition, affect, psychosis-related behavior, and sensitivity to other drugs of abuse. Animal research on psychosis and drug cross-sensitization is the most consistent with human research. Animal models may have identified molecular changes that underlie persistent emotional deficits in adults who were exposed to cannabis as adolescents. A major pitfall of animal research to date is its reliance on synthetic cannabinoids, which have different pharmacologic properties to natural cannabis. Results also vary depending on strain and dosage, the gender of the animals, and the behavioral tests used.

Despite the need for additional research, it can be concluded that clinicians should view adolescents who use cannabis as an at-risk group for cognitive difficulties and psychiatric morbidity, including suicidality. Earlier onset and heavier use indicate higher risk.

Levine A, Clemenza K, Rynn M, Lieberman J: Evidence for the risks and consequences of adolescent cannabis exposure. *Journal of the American Academy of Child and Adolescent Psychiatry* 2017;56 (March):214–225. From the College of Physicians and Surgeons, Columbia University, New York, NY; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

Biomarker for Transition to Psychosis

Low levels of erythrocyte glutathione were predictive of transition to psychosis in a small sample of high-risk adolescents and young adults. Glutathione is a major antioxidant present in the brain and cerebrospinal fluid that can be measured in blood or erythrocytes using a commercially available assay.

Background: Glutathione is the most important antioxidant defense of the brain. Low levels of glutathione in the brain have been observed in patients with schizophrenia and in those with first-episode psychosis, but they have not previously been assessed as a possible biomarker for transition in high-risk individuals. It is not clear whether peripheral glutathione levels accurately reflect status in the central nervous system. Low blood levels have been associated with the loss of cortical grey matter in patients with first-episode psychosis, and dysregulation of the antioxidant defense system in the brain is associated with dysregulation of glutamatergic and dopaminergic systems.

Methods: This analysis was conducted as part of a larger clinical trial of omega-3 fatty acids in patients, aged 13–25 years, judged to be at high risk of psychosis based on attenuated positive symptoms, transient psychosis, or genetic risk with a recent decrease in functioning. Patients received study treatment for 12 weeks and were assessed 12 months and 7 years post-randomization. The baseline assessment included measurement of erythrocyte glutathione using a commercial assay, with results expressed as $\mu\text{mol/L}$ lysate. The present analysis was limited to 36 patients in the placebo group who had glutathione measured at baseline.

Results: Of the 36 participants, 11 had transitioned to psychosis at 12 months and another 4 at the 7-year follow-up. Mean baseline glutathione levels were significantly lower in the group that transitioned at 7 years than in those who did not transition ($p < 0.001$). The comparison at 12 months was not statistically significant.

Using a cutoff value for low glutathione of $41.8 \mu\text{mol/L}$, transition at 7 years was predicted with a sensitivity* of 0.9 and a specificity* of 0.7. The positive predictive value was 83%—i.e., 10 of 12 participants with erythrocyte glutathione below the cutoff transitioned to psychosis. The negative predictive value was 79%—i.e., of 24 persons with levels above the cutoff, 19 did not transition. There was no correlation between glutathione and baseline scores on the Positive and Negative Syndrome Scale, Montgomery-Asberg Depression Rating Scale, or Global Assessment of Function.

Discussion: Based on the findings in the present sample, low glutathione may be a better predictor of long-term than short-term outcome. More research is needed to identify an ideal cutoff or a normal range.

Lavoie S, Berger M, Schlogelhofer M, Schafer M, et al: Erythrocyte glutathione levels as long-term predictor of transition to psychosis. *Translational Psychiatry* 2017; doi 10.1038/tp.2017.30. From Orygen, the National Centre of Excellence in Youth Mental Health, Parkville, Australia; and other institutions. **Funded by the Stanley Medical Research Institute; and other sources. The authors declared no competing interests.**

*See Reference Guide.

Neurocognitive Effects of Early Antibiotic Exposure

Antibiotic exposure during infancy was associated with adverse cognitive, behavioral, and emotional outcomes throughout childhood, according to a population-based longitudinal study.

Background: Data from animal models indicate that absent gut microbiota in early life is associated with increased anxiety- and depression-like behavior and increased stress reactivity, in addition to negative metabolic outcomes. Emerging clinical literature has focused mainly on the benefits of probiotic treatment during early life—e.g., it may reduce risk of ADHD.

Methods: An analysis was conducted using data from a longitudinal study of the outcome of low birth weight. The population consisted of low-birth-weight infants and normal-weight controls, all born in New Zealand between late 1995 and late 1997. All pregnancies were singleton and full-term. Data were collected at birth, 12 months, and 3.5, 7, and 11 years. Mothers were asked to report antibiotic use during each period. Assessments included the Strengths and Difficulties Questionnaire, Conners Rating Scale-Revised, Center for Epidemiologic Studies Depression Scale for children, age-appropriate IQ tests, and a standardized test of reading ability.

Results: Of 871 mother-child pairs enrolled in the study, between 493 and 550 were seen at each of the 3 childhood assessment points. A total of 27% of mothers received antibiotics during pregnancy, 70% of children received an antibiotic during their first year, and 92% received antibiotics between 1 and 3.5 years of age.

Antibiotic use in infancy was associated with poorer outcomes throughout childhood, including lower IQ scores at all ages; poorer reading ability at age 7 years; higher behavioral difficulty ratings at 3.5 and 7 years; higher parent ratings for oppositional behavior; and more depressive and ADHD symptoms at age 11 years. After adjusting for other factors that could influence outcomes, exposed children still had significantly higher parent-rated total behavioral difficulty scores at age 3.5 and 11 years ($p=0.028$ and $p=0.013$, respectively). Antibiotic use also showed a multivariate association with conduct problems at age 11 years ($p<0.0001$) and higher self-rated peer difficulties and lower self-rated prosocial behavior at age 11 years ($p=0.05$ and $p=0.044$, respectively). Eleven-year-old exposed children also had higher parent-rated and teacher-rated ADHD symptoms and higher self-rated depression symptoms.

Effect sizes* for most outcomes were small; however, those for parent- and teacher-rated ADHD and oppositional subscales of the Conners Rating Scale ADHD in 11 year olds were much larger, ranging from 1.4 to 2.8. Maternal antibiotic use during pregnancy was not associated with any adverse neurocognitive outcomes; nor was antibiotic exposure between ages 1 and 3.5.

Discussion: In the present study, the widespread use of antibiotics suggests they were being prescribed for minor conditions; therefore the adverse effects cannot be explained by serious underlying infections.

Slykerman R, Thompson J, Waldie K, Murphy R, et al: Antibiotics in the first year of life and subsequent neurocognitive outcomes. *Acta Paediatrica* 2017;106 (January):87–94. From the University of Auckland, New Zealand. **Funded by the Health Research Council of New Zealand; and other sources. The authors declared no competing interests.**

*See Reference Guide.

Melatonin and Antipsychotic-Related Weight Gain

In a placebo-controlled trial of adolescents with bipolar disorder, coadministering melatonin modestly attenuated weight associated with olanzapine (*Zyprexa*) and lithium treatment.¹

Background: Melatonin regulates circadian rhythms and may have beneficial effects on sleep and mood, which in turn may influence food intake, metabolism, and weight. Melatonin has beneficial effects on body composition in animal models, including rats given olanzapine, and it has possible cardiovascular and metabolic health benefits in human adults. A single study of melatonin in adults with schizophrenia found that it limited olanzapine-related weight gain.²

Methods: Study subjects were 48 patients, aged 11–17 years, with a new diagnosis of DSM-IV-TR bipolar I disorder. Participants had baseline weight in the normal range, with a body mass index (BMI) between 18 and 25, and did not have an eating disorder. All patients received 5–10 mg/day olanzapine and lithium based on therapeutic blood levels. They were also randomly assigned to receive 3 mg/day melatonin or placebo. Weight and height were measured again after 6 and 12 weeks of treatment.

Results: Patients had an average age of 14.5 years and a mean baseline BMI of about 20. Five patients in the placebo group and 3 in the melatonin group stopped their psychotropic medication during the study because of weight gain, and 2 in the melatonin group were lost to follow-up, leaving 19 in each group. Among these patients, the mean increase in BMI was 2.45 in the melatonin group, compared with 3.25 in the placebo group ($p=0.061$). Patients gained a mean of 13 lbs with melatonin, compared with 18 lbs with placebo ($p=0.065$). Adjusting the analysis to account for baseline weight did not affect the results.

Discussion: Weight gain is among the most troublesome adverse effects of psychotropic treatment. Although the between-group difference in weight gain was not statistically significant in this study, the sample size was small and the 5-lb difference in weight gain with melatonin over 3 months may be clinically relevant.

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

¹Mostafavi S-A, Solhi M, Mohammadi M-R, Akhondzadeh S: Melatonin for reducing weight gain following administration of atypical antipsychotic olanzapine for adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Child and Adolescent Psychopharmacology* 2017; doi 10.1089/cap.2016.0046. From Tehran University of Medical Sciences, Iran. **Funded by the university. The authors declared no competing interests.**

²Modabbernia A, et al: Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: randomized double-blind placebo-controlled study. *Journal of Psychiatric Research* 2014;53:133–140.

*See Reference Guide.

Reference Guide

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.

Sensitivity and Specificity: Statistical measures of the performance of binary classification tests. Sensitivity measures the proportion of actual positives that are correctly identified (i.e., the percentage of sick people who are correctly identified as having the condition). Specificity 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). A perfect predictor would have 100% sensitivity and specificity.

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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First Suicide Attempt: Risk Factors and Outcomes

According to the results of a population-based longitudinal study, risk factors for a first suicide attempt differ depending on whether the attempter is a child or an adolescent. Adult mental-health outcomes also differ between the 2 groups, with worse outcomes for those who attempt suicide at a younger age.

Methods: Data were obtained from the National Epidemiologic Survey on Alcohol and Related Conditions, a face-to-face survey of U.S. adults conducted by the National Institute on Alcohol Abuse and Alcoholism. Interviews were conducted in 2 waves in the early 2000s, and the analysis was weighted to reflect the 2000 U.S. census population. All respondents were asked to report any suicide attempts; those reporting an attempt at age ≤ 12 years were classified as child attempters, and those at ages 13–17 years as adolescent attempters. Respondents were also evaluated using standardized measures of DSM-IV Axis I and II disorders and health-related quality of life. Participants were asked about childhood traumatic experiences, including being sexually attacked or molested or experiencing unwanted sex, physical abuse, neglect, and having seen serious fights at home. Five types of maltreatment were examined using standardized questions: emotional neglect, physical neglect, emotional abuse, physical abuse, and sexual abuse.

Results: Of >34,000 adults who participated in both waves, 104 (0.27%) reported a first suicide attempt during childhood and 415 (1.22%) during adolescence. There was a significant increase in the rate of a first attempt between ages 12 and 13 years ($p < 0.001$), indicating that this was a suitable cutoff between child and adolescent age groups. There was no difference in the ratio of male to female attempters between the child and adolescent age groups.

Participants who first attempted suicide during adolescence had a higher prevalence of major depressive disorder before the attempt than those who attempted suicide at a younger age. (See table, next page.) In contrast, children who made a suicide attempt had significantly increased rates of traumatic experiences and several types of maltreatment.

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Contributing factors for a first suicide attempt in children and adolescents			
Factor	Prevalence in children (n=104), weighted	Prevalence in adolescents (n=415), weighted	Adjusted significance for difference
Major depressive episode	6.5%	21.7%	p=0.001
<i>Traumatic Experiences</i>			
Attack by parent	33.7%	19.0%	p=0.012
Serious neglect	36.6%	14.9%	p<0.001
<i>Type of Maltreatment</i>			
Physical neglect	10.2%	8.0%	p<0.001
Emotional abuse	9.2%	7.4%	p<0.001
Physical abuse	6.1%	4.6%	p<0.001
Sexual abuse	8.5%	6.9%	p=0.014

As adults, child suicide attempters had increased rates of manic or hypomanic disorder (45% vs 30%; p=0.02) and of panic disorder with or without agoraphobia (42% vs 27%; p=0.01). They also had significantly lower scores on a measure of social functioning. Those who first attempted suicide during childhood had a higher rate of ≥ 1 recurrent attempt than those who first attempted suicide during adolescence (adjusted odds ratio,* 3.6). The overall population of child and adolescent suicide attempters had higher rates of nearly all lifetime and recent psychiatric disorders, greater exposure to traumatic experiences before age 18 years, and parental history of mental-health disorders, as well as poorer health-related quality of life.

Discussion: Maltreatment was a strong risk factor for predicting suicide attempts in both age groups and should be assessed in all young persons who attempt suicide. Preventing child maltreatment with evidence-based interventions could decrease the risk of suicide attempts. Children and adolescents who attempt suicide should be followed closely to prevent the risk of a repeat attempt and the emergence of mental-health disorders in adulthood.

Peyre H, Hoertel N, Stordeur C, Lebeau G, et al: Contributing factors and mental health outcomes of first suicide attempt during childhood and adolescence: results from a nationally representative study. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.16m10876. From Robert Debre Hospital, Paris, France; and other institutions. **This study was conducted with no direct funding. Two study authors disclosed financial relationships with commercial sources; the remaining 8 authors declared no competing interests.**

*See Reference Guide.

Individual vs Family-Focused Therapy for Depression

In a randomized trial, family-focused therapy was superior to individual supportive psychotherapy (IP) in children with depression, although both treatments produced improvement.¹

Methods: The authors of this study developed Family-Focused Treatment for Childhood Depression (FFT-CD), and its efficacy was demonstrated in an earlier phase 1 trial.² In the present study, FFT-CD was compared with IP in children, aged 7–14 years, with major depressive disorder, dysthymic disorder, or depressive disorder—not otherwise specified. Both treatments were delivered by the same therapists and were of the same intensity: 15 hour-long sessions over a period of ≤ 22 weeks. FFT-CD consisted of cognitive-behavioral and family interventions designed to target the interplay of mood and interpersonal interactions within the family and teach skills to improve family functioning and reduce stress. IP was based on manualized Client-Centered Therapy and consisted of weekly individual sessions, with occasional brief parent meetings. The study's primary efficacy outcome was adequate clinical depression response, defined as a $\geq 50\%$ reduction in the Children's Depression Rating Scale, Revised (CDRS-R) score from baseline to post-treatment. Remission was defined as a CDRS-R score of ≤ 28 .

Results: A total of 134 children were randomized, and 116 (87%) completed post-treatment assessment. Rates of treatment dropout were comparable in the 2 groups, with 14% dropping out before 5 sessions and another 12% before 10 sessions. Children had a mean age of about 11 years, slightly over half were girls, and they represented a range of ethnicity and family incomes.

In the overall population, adequate response occurred in 78% of children receiving FFT-CD and in 60% of those receiving IP (odds ratio [OR],* 2.29; number needed to treat [NNT],*6; $p < 0.05$). The between-group difference in remission did not reach statistical significance, but was significant in an analysis limited to children who completed treatment: 54% for FFT-CD vs 36% for IP (OR, 2.11; NNT, 6; $p < 0.05$). Results were robust when the analysis was limited to children in the preadolescent age range of 7–12 years.

Parents and children reported similar overall satisfaction for both treatments. Between-group differences in several patient-centered outcomes favored FFT-CD, including parents' reports that therapy helped them understand how to manage their child's depression ($p = 0.01$) and how to help the child at home ($p < 0.001$), and children's reports that they were better able to get along with their family ($p = 0.04$) and deal with problems ($p = 0.05$). Secondary illness-related outcomes, including additional measures of depression severity, functioning, and comorbid symptoms, did not differ between treatments.

¹Tompson M, Sugar C, Langer D, Asarnow J: A randomized clinical trial comparing family-focused treatment and individual supportive therapy for depression in childhood and early adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry* 2017; doi 10.1016/j.jaac.2017.03.018. From Boston University, MA, and the University of California, Los Angeles. **Funded by the NIMH. The study authors declared no financial relationships with pharmaceutical-industry sources.**

²Tompson M, et al: Family-focused treatment for childhood-onset depressive disorders: results of an open trial. *Journal of Clinical Child Psychology and Psychiatry* 2007;12:403–420.

*See Reference Guide.

Trends in Bullying

The prevalence of school-based bullying has decreased over the past 10 years, according to a longitudinal survey of Maryland school-aged children and adolescents. Contrary to a common public assumption, cyberbullying has become less prevalent, although that may change rapidly with technological innovations and new social media platforms.

Background: Bullying, as defined by the Centers for Disease Control and Prevention, is intentional aggressive behavior that occurs in the context of a power differential and is repeated or has the potential to be repeated. Multiple studies have demonstrated a negative impact of bullying on mental health, as well as behavioral, academic and health outcomes.

Methods: Study participants were enrolled in grades 4–12 in 109 schools in a single district: 78 elementary schools, 19 middle schools, and 12 high schools. For 10 consecutive years, from 2005 to 2014, students were asked to complete an anonymous online questionnaire on school computers during school hours. The main indicator of bullying was whether a student had frequently (i.e., twice in the past month) experienced or perpetrated bullying. Participants were also asked whether they had seen someone else being bullied, to what degree they agreed with attitude statements about bullying, and their perceptions of safety and belonging at school.

Results: A total of nearly 250,000 questionnaires were completed. The overall prevalence of frequent victimization by bullying decreased from 28% to 13% over the 10 years ($p < 0.001$; effect size,* 0.33), with significant decreases in all specific indicators: being pushed, hit, threatened, having rumors spread, and cyberbullying. There were also significant decreases in frequently bullying others (21%–7%; $p < 0.001$; effect size, 0.35) and in witnessing bullying

(66%–43%; $p < 0.001$; effect size, 0.50), and a modest improvement in the belief that adults did enough to stop bullying. Throughout the 10 years, an unchanging proportion of students, about half, agreed that bullying was a problem. More students reported that they felt safe at school (79%–88%; $p < 0.001$; effect size, 0.24), but there was little change in students' feeling of belonging (about 80% throughout). The declines in bullying were largest in recent years, possibly reflecting the effect of new bullying policies and evidence-based anti-bullying programs.

Bullying was less of a concern among elementary school children than those in middle and high school, and they reported relatively modest changes over time compared with middle schoolers. Those in high school reported larger improvement in feelings of safety and larger decreases in witnessing bullying than middle schoolers.

Discussion: This study indicates that bullying remains prevalent but is declining in school-aged youth. The prevalence of cyberbullying was consistently $< 10\%$, in line with federal government agencies' estimates. High schools showed the most improvement in bullying over time; and more improvement is needed in middle school, where bullying peaks.

Waasdorp T, Pas E, Zablotsky B, Bradshaw C: Ten-year trends in bullying and related attitudes among 4th- to 12th-graders. *Pediatrics* 2017; doi 10.1542/peds.2016-2615. From Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; and other institutions. **Funded by the US Department of Education; and other sources. The authors declared no competing interests.**

*See Reference Guide.

Habit Reversal Training for Trichotillomania

In a preliminary randomized trial, habit reversal training (HRT) was superior to treatment as usual (TAU) in children and adolescents with trichotillomania. HRT is a well-established treatment for hair pulling and other habit disorders in adults but has received little study in younger patients, although hair pulling symptoms usually first appear during childhood and adolescence.

Methods: Study participants ($n=40$; mean age, 12 years) met DSM-IV criteria for a primary diagnosis of trichotillomania and were randomly assigned to receive either HRT or TAU. Hair-pulling behavior was measured by blinded evaluators with the 7-item Massachusetts General Hospital Hair Pulling Scale (MGH-HPS) and the 6-item National Institute of Mental Health–Trichotillomania Severity Scale (NIMH-TSS). HRT was delivered in 8 weekly individual sessions that provided awareness training, training in competing behaviors to replace the hair pulling, and social support. Control patients were instructed to continue receiving their previous treatments, including medications, psychotherapy, or school-based/other interventions. Modifications and new interventions were permitted. Of the 19 patients assigned to TAU, 10 received no outside treatment.

Results: At the end of treatment, patients who received HRT demonstrated a significant, large improvement from baseline in the mean NIMH-TSS score (effect size,* 1.31; $p < 0.001$), as well as a large difference from the TAU group (effect size, 0.87). Patients in the control group had a small, nonsignificant average decrease from baseline in the NIMH-TSS (effect size, 0.31). Results were similar measuring change from baseline in the MGH-HPS (HRT: effect size, 1.34; $p < 0.001$; TAU: effect size, 0.34; $p = \text{ns}$). According to Clinical Global Impression–Improvement ratings, 16 of 21 patients experienced response to HRT, compared with 4 of 19 controls (76% vs 21%; $p < 0.001$). Of the initial responders to HRT who participated in follow-up, 10 of 12 continued to meet response criteria at 1 month. At 3 months, 6 of 8 available patients had sustained response.

Participants in the TAU group were offered open-label HRT at study end. In the combined group of 38 patients who received HRT, there were large reductions in symptom severity (effect sizes, 1.21–1.38) and 31 patients (82%) were considered responders to treatment.

Discussion: Trichotillomania is a challenge to treat because the disorder is chronic and patients often relapse. It is possible that treating the disorder in youth may mitigate its course. Strategies typically involve behavioral treatments, primarily HRT, with a smaller role for medications. Enhancement of HRT with acceptance and commitment therapy or dialectical behavioral therapy is effective in adults and should be evaluated in young people. The finding in this study that a substantial portion of patients (25%) who initially responded to HRT did not sustain response at 3 months suggests that booster sessions may be necessary.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial; however, the source of funding was not disclosed.

Rahman O, McGuire J, Storch E, Lewin A: Preliminary randomized controlled trial of habit reversal training for treatment of hair pulling in youth. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (March):132–139. From the University of South Florida, Tampa; and other institutions. **Source of funding not stated. All study authors disclosed financial relationships with commercial sources; however, none appear to be relevant to the current study.**

*See Reference Guide.

Educational Outcomes in ADHD

According to a Scottish national population-based cohort study, children and adolescents who received treatment for ADHD had worse outcomes than their unaffected peers on a range of educational and health outcomes.

Methods: Study data were aggregated from countrywide health and school databases that included all individuals between the ages of 4 and 19 years who were in school between 2009 and 2013. The exposed group consisted of children who received any of 4 medications approved solely for the treatment of ADHD: methylphenidate, dextroamphetamine, atomoxetine, or lisdexamfetamine. Educational and other outcomes were compared between exposed and unexposed children. Analyses of academic attainment and employment were limited to those who left school during the study period.

Results: The analysis included a total of >766,000 children and adolescents. Of these, 7413 (1%) received ADHD medication. These children were more likely than others to be male, socioeconomically deprived, and to have a variety of birth-related risk factors and a history of learning disability, autism, and early school leaving.

Children receiving ADHD medications had increased rates of all of the adverse outcomes, which were statistically significant in univariate analyses and attenuated, but still significant, after adjusting for all available socioeconomic, demographic, obstetric, and health-related risk factors. (See table.) For most adverse outcomes, the effect of being treated for ADHD was larger for girls than boys and smaller for children living in socioeconomically deprived areas, a group that had higher overall rates of these problems regardless of ADHD. Children

Association between ADHD medication and adverse educational outcomes	
Outcome	Adjusted Risk
Unauthorized absence from school	Incidence rate ratio,* 1.16
School exclusion	Incidence rate ratio, 5.79
Special educational needs	Odds ratio,* 8.62
Poorer academic attainment	Odds ratio, 3.35
Unemployment after leaving school	Odds ratio, 1.39
Hospitalization	Hazard ratio,* 1.25

receiving ADHD medication had higher rates of each type of special educational need: those involving mental health; social, emotional, and behavioral problems; learning disability; physical health; physical or motor impairment; learning difficulty; communication problems; and sensory impairment. Treatment for ADHD was also associated with higher rates of hospitalization, with injury the most common reason for hospital admission (14% of admissions; adjusted hazard ratio, 1.52).

Discussion: Even while receiving treatment, young people with ADHD fare significantly worse across a variety of academic and health outcomes than their unaffected peers. The authors note that in Scotland, the proportion of children who receive a diagnosis of ADHD and receive treatment varies by region (0.2%–1.2% of the population) and that 70%–96% of Scottish children with ADHD do not receive medication. Therefore, the exposed group in the study likely comprised children with more severe ADHD, and the comparison group may have included some children with less severe or undiagnosed symptoms.

Fleming M, Fitton C, Steiner M, McLay J, et al: Educational and health outcomes of children treated for attention-deficit/hyperactivity disorder. *JAMA Pediatrics* 2017; doi 10.1001/jamapediatrics.2017.0691. From the University of Glasgow, Scotland; and other institutions. **Funded by the Farr Institute of Health Informatics Research; and other sources. The authors declared no competing interests.**

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

*See Reference Guide.

Reference Guide

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.

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.

Rate Ratio: A comparison of the rates of a disease/event in 2 groups that differ by demographic characteristics or exposure history. The rate for the group of primary interest is divided by the rate for a 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.

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New ADHD Treatments Approved

The FDA has approved the first generic atomoxetine (*Strattera*) products to treat ADHD in adults and children.¹ The generics, manufactured by 4 pharmaceutical companies, will be available in multiple strengths and carry the same Medication Guide requirement as the branded product.

Also approved is a new extended-release orally disintegrating methylphenidate formulation (*Cotempla XR-ODT*).² In clinical trials, *Cotempla XR-ODT* had onset of action at 1 hour post-dose and lasted through 12 hours. Adverse effects were consistent with the known profile for other extended-release methylphenidate products. The new formulation, as with other CNS stimulants, has high abuse and dependence potential and is approved as a controlled substance.

¹FDA News Release: FDA approves first generic Strattera for the treatment of ADHD. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm561096.htm.

²Neos therapeutics announces FDA approval of Cotempla XR-ODT™ (methylphenidate) extended-release orally disintegrating tablets for the treatment of ADHD in patients 6 to 17 years old [press release]. Dallas and Fort Worth, TX: Neos Therapeutics Inc.; June 19, 2017. Available at <http://investors.neostx.com/phoenix.zhtml?c=254075&p=RssLanding&cat=news&id=2281776>.

Prenatal Antidepressant Exposure and ADHD

A large, population-based cohort study confirmed the association between ADHD and prenatal exposure to antidepressants, but with a smaller effect than shown in previous reports.¹ The association may be at least partly the result of confounding by indication—i.e., shared family factors that contribute to both maternal depression and ADHD in the offspring.

Background: Recent epidemiologic studies, conducted in North America and Scandinavia, suggest ADHD may be related to maternal antidepressant use, but results have been conflicting. Children aged <5 years were overrepresented in the studies (an ADHD diagnosis is usually made at an older age), and investigators failed to account for confounding by maternal risk factors.

Methods: The present study was conducted using a database of all children born in Hong Kong between 2001 and 2009. Children were followed until the end of 2015; thus all had ≥6 years of

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follow-up. Mothers were classified as gestational antidepressant users or nonusers. Non-gestational users were further classified as those who used antidepressants before pregnancy but stopped when they became pregnant and those who had never used antidepressants. This latter group was further subdivided into women with or without a psychiatric disorder.

Results: The analysis included >190,000 mother-child pairs; 1252 children were exposed to antidepressants in utero. Of 2275 mothers who received antidepressants before pregnancy, 1486 had stopped the drugs and 789 had continued into pregnancy.

A total of 5659 children received a diagnosis of ADHD or medication for ADHD, at an average age of >9 years. Antidepressant use during pregnancy was associated with increased risk of ADHD (hazard ratio,* 2.39; $p < 0.01$) after adjustment for multiple demographic, medical, and socioeconomic factors. When the model was further adjusted for maternal depression and other psychiatric drug use, the risk estimate was reduced (hazard ratio, 1.39; $p = 0.01$), but remained statistically significant. In the fully adjusted model, ADHD risk was similar for exposure during each of the pregnancy trimesters (hazard ratios, 1.43–1.5) and was somewhat higher with non-SSRIs than SSRIs (hazard ratios, 1.59 vs 1.11).

Risk of ADHD was higher in children whose mothers stopped taking antidepressants upon becoming pregnant, compared with never users (hazard ratio, 1.76), and higher in women who never used antidepressants but had a psychiatric disorder diagnosed before or during pregnancy, compared with those with no disorder (hazard ratios, 1.96–2.02). Risk did not differ between children of mothers who received treatment with an antidepressant versus an antipsychotic or in gestational users versus preconceptional users.

Discussion: Results of this study provide strong support for confounding by indication as the underlying factor in the association, because risk was consistently increased in gestational users for all 3 trimesters, in preconception users, and in non-users with a psychiatric diagnosis.

Editorial.² Although experiments in animals suggest causality is biologically plausible, there is no way to determine causality based on the present study results. However, regardless of whether the association is causal, use of antidepressants in pregnancy is a marker for various pregnancy risks and adverse mental health outcomes in offspring, including ADHD.

¹Man K, Chan E, Ip P, Coghill D, et al: Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study. *BMJ* 2017; doi 10.1136/bmj.j2350. From the University of Hong Kong, China; and other institutions. **This study was conducted without funding. Seven of 10 study authors declared financial relationships commercial sources; the remaining authors declared no competing interests.**

²Pedersen L: The safety of antidepressants in pregnancy [editorial]. *BMJ* 2017; doi 10.1136/bmj.j2544. From Aarhus University, Denmark. **The author declared no competing interests.**

*See Reference Guide.

Throat Infections and Psychiatric Disorders

In a nationwide Danish cohort study, risk of psychiatric disorders—particularly OCD and tic disorders—was elevated in children and adolescents with a prior streptococcal throat infection. Risk was also increased, but to a lesser extent, in children with non-strep throat infections.

Methods: Data were extracted from Danish national health and psychiatric registries for citizens born in 1996–2013. All patients with a record of a rapid antigen diagnostic test for group A β -hemolytic streptococcus were presumed to have a throat infection. The database did not record whether a test result was positive or negative. Hence, only patients who filled a prescription for an antibiotic within 8 days of the test were presumed to have a positive result.

Results: The database included >1 million individuals born during the study years and followed for a maximum of 17 years. More than 638,000 were tested for streptococcal infection, and nearly 350,000 (55%) had a positive result. During the study period, >40,000 patients received a mental

health diagnosis, including 1078 with OCD and 2177 with a tic disorder. Compared with patients who were not tested, risks of all psychiatric disorders and of OCD and tic disorders were significantly elevated in patients who tested positive for a streptococcal infection. (See table.) Risks were also significantly elevated, but to a lesser degree, in those who were tested and found negative.

After the OCD and tic diagnostic categories were removed from the data, a positive streptococcal result was also associated with

Adjusted risk (incidence risk ratio) of mental disorders in Danish children and adolescents tested for streptococcal infection, compared with untested children			
	Any Mental Disorder	OCD	Tic Disorder
Negative test	1.07	1.27	1.24
Positive test	1.16	1.49	1.34

increased risk for adult personality and behavior disorders as well as mood disorders (incidence rate ratios,* 1.85 and 1.64, respectively). Risk of OCD and tic disorders increased in a linear fashion with an increasing number of positive tests and also with increasing negative tests. Risk appeared to increase throughout the time after a positive test, rather than peaking shortly after the infection. Children with a positive test had a nearly 2-fold higher risk of OCD compared with their siblings who had a negative test result.

Discussion: The PANDAS hypothesis, that antistreptococcal antibodies cross-react with the basal ganglia of the brain to cause psychiatric illness, remains controversial. The present study supports the PANDAS hypothesis to some extent and agrees with several prior studies showing a positive association and a dose-response relationship. The results suggest that other, viral infections are also linked with the development of OCD and tic disorders, in line with the broader, recently proposed diagnostic category of pediatric acute-onset neuropsychiatric syndrome (PANS). Alternative explanations for the association include increased medical-care seeking behavior by some parents and a shared genetic or socioeconomic susceptibility to infections and mental disorders.

Orlovská S, Vestergaard C, Bech B, Nordentoft M, et al: Association of streptococcal throat infection with mental disorders: testing key aspects of the PANDAS hypothesis in a nationwide study. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.0995. From the University of Copenhagen, Denmark; and other institutions. **Funded by the Lundbeck Foundation; and the Novo Nordisk Foundation. The authors declared no competing interests.**

*See Reference Guide.

Bipolar vs Unipolar Depression

Young people experiencing a depressive episode of bipolar disorder have a distinct symptom profile relative to those with unipolar depression, with more atypical depressive symptoms and subsyndromal manic symptoms.

Methods: Participants were enrolled in 2 longitudinal studies conducted by the same investigators using similar methods: the Course and Outcome of Bipolar Youth study and the Neurobehavioral Changes in Pediatric Affective Disorder study. The comparison was limited to patients who were experiencing a current depressive episode at the time of study intake and assessment. Participants were evaluated using various versions of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS), as well as the Depression Rating Scale (DRS) and Mania Rating Scale (MRS), which were derived from the original K-SADS-Present version.

Results: A total of 30 patients with bipolar depression and 59 with unipolar depression were included in the study. Those with a bipolar diagnosis were older on average (mean age, 15 vs

12 years; $p < 0.0001$) and had higher rates of Axis-I comorbidity (97% vs 52%; $p < 0.0001$), with significantly higher prevalence of ADHD, disruptive behavior disorders, anxiety disorders, and psychotic symptoms.

Among depressive symptoms, 3 distinguished particularly well between the 2 groups. Young people with bipolar depression had significantly higher rates of moderate-to-severe mood reactivity (odds ratio [OR]*, 9.7) and nonsuicidal self-injury (OR, 17.2) and a lower rate of reported aches and pains (OR, 0.1). Those with bipolar depression also had higher prevalence of moderate-to-severe diurnal mood variation, hopelessness, anhedonia, fatigue, psychomotor agitation, social withdrawal, daytime sleepiness, strong craving for sweets, and lethality of suicidal acts.

All of the manic symptoms rated by the MRS, except for increased goal-directed activity, were significantly associated with bipolar depression; those rated by the investigators as having the highest probability of discriminating include distractibility (OR, 37.8), pressured speech (OR, 28.9), racing thoughts (OR, 21.7), and elation (OR, 15.2). One manic symptom, irritability/anger, was less likely to affect youth with bipolar disorder than those with unipolar depression (OR,* 0.1; $p = 0.02$). The mean number of subsyndromal manic symptoms was higher in young people with bipolar depression (8.4 vs 1.7; $p < 0.0001$). There were too few participants with bipolar disorder to identify symptoms that might distinguish between the bipolar subtypes.

Discussion: Careful characterization of mood symptoms in young people who present with depression can help differentiate unipolar from bipolar depression and possibly decrease the long diagnostic delays that characterize the latter. Clinicians should pay special attention to the presence of mood reactivity, nonsuicidal self-injury, and aches and pains. It is particularly important to screen for subsyndromal manic symptoms, which are highly specific to bipolar disorder and which also predict safety risk and poor clinical outcome.

Diler R, Goldstein T, Hafeman D, Merranko J, et al: Distinguishing bipolar depression from unipolar depression in youth: preliminary findings. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (May):310–319. From the University of Pittsburgh School of Medicine, PA; and other institutions. **Funded by the NIMH. Three of the 16 study authors disclosed financial relationships with pharmaceutical-industry sources.**

*See Reference Guide.

Depression Treatment in Bipolar Disorder

Treatment recommendations for depressive symptoms in pediatric bipolar disorder generally parallel those in adults, according to a literature review. The published evidence supports high-dose quetiapine for depressive symptoms during mixed bipolar episodes and olanzapine plus fluoxetine for bipolar depression.

Methods: The investigators identified studies—i.e., clinical trials, open-label studies, retrospective chart reviews, systematic reviews, and meta-analyses—published in English and limited to patients aged <18 years, that evaluated pharmacotherapy for depressive symptoms in pediatric bipolar disorder. The review included 45 studies that measured the effects of atypical antipsychotics or mood stabilizers and reported the results using standardized rating scales. Most studies were conducted in patients with mixed or manic states; only 4 were limited to adolescents with bipolar depression. The evidence was classified using the Oxford Centre for Evidence-based Medicine's Levels of Evidence I. (See table, next page.)

Results: The review did not identify any level 1a evidence. Level 1b evidence indicates that quetiapine monotherapy reduces depressive symptoms in the acute phase of bipolar I disorder in children with current mania or mixed mania. The evidence is heterogeneous because of differences between studies in dosing and diagnosis. A 600-mg/day dosage was effective, but

dosages of ≤ 400 mg/day were not. In addition, quetiapine was not effective in a study limited to patients with bipolar depression rather than mania or mixed mania. At present, quetiapine is FDA approved for manic episodes in bipolar I disorder in patients aged ≥ 10 years.

Level 1b evidence also supports the efficacy of olanzapine–fluoxetine in reducing depressive symptoms, with an effect size* of 0.46 compared with placebo. Weight gain was generally a significant side effect in the olanzapine trials. The combination is FDA approved for acute treatment of bipolar I depression in patients aged 10–17 years.

Among the remaining atypical antipsychotics, the authors found no convincing evidence of antidepressant efficacy for monotherapy with aripiprazole, olanzapine, risperidone, or ziprasidone. They recommend additional investigation of the potential of aripiprazole in combination therapy, given its superior tolerability. For the other atypicals, evidence is either contradictory or limited to a low level. Lurasidone, approved for treating bipolar depression in adults, has not yet been studied in children and adolescents.

According to Level 1b evidence, lithium monotherapy does not have antidepressant efficacy in pediatric bipolar disorder; however, numerous studies with weaker designs suggest it might be effective when combined with valproate or an atypical antipsychotic. The evidence is mixed regarding valproate and carbamazepine as monotherapy. Weak evidence (Level 2b) suggests possible efficacy for lamotrigine and for the combination of olanzapine with topiramate.

Atkin T, Nunez N, Gobbi G: Practitioner review: the effects of atypical antipsychotics and mood stabilisers in the treatment of depressive symptoms in paediatric bipolar disorder. *Journal of Child Psychology and Psychiatry* 2017; doi 10.1111/jcpp.12735. From McGill University, Canada. **Funded by the Quebec Network on Suicide, Mood Disorders and Related Disorders; and the Canadian Depression Research & Intervention Network. The authors declared no competing interests.**

Common Drug Trade Names: aripiprazole—*Abilify*; carbamazepine—*Tegretol*; lamotrigine—*Lamictal*; lurasidone—*Latuda*; olanzapine—*Zyprexa*; olanzapine–fluoxetine—*Symbyax*; quetiapine—*Seroquel*; risperidone—*Risperdal*; topiramate—*Topamax*; valproate—*Depakene, Depakote*; ziprasidone—*Geodon*

*See Reference Guide.

Oxford Centre for Evidence-based Medicine's Levels of Evidence

Level 1a: A systematic review with homogeneity of randomized controlled trials

Level 1b: An individual randomized controlled trial with a narrow confidence interval

Level 2a: A systematic review with homogeneity of cohort studies

Level 2b: An individual cohort study, including low-quality randomized controlled trials (e.g. $<80\%$ follow-up)

Level 3a: A systematic review with homogeneity of case-control studies

Level 3b: An individual case-control study

Parent Training for Disruptive Behaviors

Technological approaches have long been available to address barriers to treatment for behavior disorders. However, research on present-day technology is limited. According to a systematic review, digitally assisted parent training programs improve child outcomes and can reduce professional burden, thus potentially improving accessibility to evidence-based treatments for disruptive behavior disorders.

The review identified 14 studies of 10 different digital interventions (e.g., Parenting Wisely/ Parenting ToolKit, Triple P, Comet, Helping the Noncompliant Child) with a total of 2427 participants, of whom 1500 received digital interventions. Most studies ($n=10$) were aimed at children, mainly those aged <9 years; 4 studies targeted older children and adolescents. All of the programs focused on behavioral approaches, in which parents learned skills to modify their interaction with their child. Four programs were primarily noninteractive, consisting of an unmodifiable series of videos or audio podcasts, and the rest were interactive, with participants able to navigate through the program's offerings. Program components included instructional videos; multiple-choice questions with direct feedback; platform support; notifications and reminders; online peer discussions; and in 1 case, video-

taped home practice that was reviewed by a therapist. Of the 10 programs, 7 were entirely self-directed and 3 were combined with professional support—e.g., telephone calls, monitoring, and coaching.

Treatment participation and completion were on a par with rates previously described for in-person interventions; about 80% of participants completed the digitally assisted programs. All of the studies reported post-treatment improvements, although it was not possible to estimate an overall effect because of large differences in the programs and target populations. In young children whose parents received self-directed interventions (4 studies), effect sizes* ranged from 0.47 to 0.80. Effect sizes for programs targeting adolescents were smaller but statistically significant (0.17–0.20). When digital and therapist-led treatments were compared, there were no differences in outcomes.

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

Baumel A, Pawar A, Mathur N, Kane J, et al: Technology-assisted parent training programs for children and adolescents with disruptive behaviors: a systematic review. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.16r11063. From Zucker Hillside Hospital, Glen Oaks, NY; and other institutions. **This study was conducted without direct funding. Two study authors disclosed financial relationships with commercial sources; the remaining 3 authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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.

Incidence rate ratio: The number of new cases of a condition in a defined (specified) group or population expressed as a ratio—if there are 1000 people and a condition develops in 14 of them, the incidence rate is 14 per 1000 or 1.4%.

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.

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Brief Anxiety Therapies

In a randomized trial, efficacy was similar for parent-delivered cognitive behavioral therapy (CBT) and solution-focused brief therapy in children with anxiety symptoms; however, parent-delivered CBT was more cost-effective.

Methods: The study, conducted in 4 primary child and adolescent mental-health clinics in the U.K., enrolled families referred for treatment of a child, aged 5–12 years, with clinically impairing anxiety. Children were not required to meet specific diagnostic criteria for an anxiety disorder. Those taking psychotropic medication were excluded from the study. Parent-delivered CBT was provided in the form of a self-help book and ≤ 8 weekly sessions of therapist support, totaling 5 hours. Four of the sessions were face to face, and 4 were brief telephone reviews lasting about 15 minutes. The comparison treatment, solution-focused brief therapy, was provided based on usual practice in the clinics. It also consisted of 5 hours of therapist contact, with 6 face-to-face sessions with the child and parent or the child alone. Both treatments were provided by the same therapists. Outcomes were assessed by an independent rater based on interviews conducted at the patients' homes at baseline, after treatment, and at 6-month follow-up. The primary outcome was recovery, defined as a Clinical Global Impression–Improvement rating of much or very much improved. The study also included an economic evaluation based on all societal costs of the treatments.

Results: A total of 136 children were randomized and received treatment. At baseline, 90% had an anxiety-disorder diagnosis. Outcomes of the 2 treatments did not differ statistically: 59% and 69% of the parent-delivered CBT and solution-focused brief therapy groups, respectively, met recovery criteria after treatment, and 66% and 72%, respectively, met the criteria at 6 months. At least half of patients in each group no longer met criteria for a primary anxiety-disorder diagnosis at both time points.

Overall costs were nearly 25% lower for parent-delivered CBT than for solution-focused brief therapy. The main drivers of this cost savings were related to the reduction in face-to-face

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sessions, decreasing travel and time lost from other activities by the therapists and additional time taken from school or work by parents and children.

Discussion: Evidence-based psychological treatments for anxiety are typically lengthy, with 14–16 hour-long sessions. Results of this study show that brief interventions can have similar effects. Rather than an inactive control condition, solution-focused brief therapy was chosen as the comparator to CBT because it is widely used in mental-health settings in the U.K.

Editorial.² The treatment modalities evaluated in this study require little therapist training and can be widely incorporated in practice. Brief telephone contacts are a way to extend the reach of treatment, using a familiar non-intimidating form of technology.

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

¹Creswell C, Violato M, Fairbanks H, White E, et al: Clinical outcomes and cost-effectiveness of brief guided parent-delivered cognitive behavioural therapy and solution-focused brief therapy for treatment of childhood anxiety disorders: a randomised controlled trial. *Lancet* 2017; doi 10.1016/S2215-0366(17)30816-4. From the University of Reading, U.K.; and other institutions. **Funded by the National Institute for Health Research. One study author disclosed a relevant financial relationship; the remaining 7 authors declared no competing interests.**

²Stallard P: Low-intensity interventions for anxiety disorders [editorial]. *Lancet* 2017; doi 10.1016/s2215-0366(17)30186-4. From the University of Bath, U.K. **The author declared no competing interests.**

*See Reference Guide.

SSRIs and Adiposity

In an observational study of older adolescents with depression, SSRI therapy was associated with increased adiposity while depression severity was associated with weight loss. The effect of SSRIs was particularly pronounced for citalopram and escitalopram.

Background: Obesity and major depressive disorder are thought to exacerbate each other due to dysregulation of the hypothalamic-pituitary-adrenal axis and other factors including lifestyle. Most studies of the relationship have not accounted for the effect of medications or have not measured adiposity in a precise fashion.

Methods: Study participants were healthy 15–20-year-old individuals either without depression or with depression that was unmedicated or treated with an SSRI starting within the previous month. Those taking other antidepressants or with an eating disorder were excluded. Every 4 months for 2 years, patients underwent follow-up assessments, which included evaluation of depressive symptoms with the Inventory of Depressive Symptomatology (IDS) and the Beck Depression Inventory (BDI), anxiety symptoms with the Beck Anxiety Inventory (BAI), physical activity, height, weight, and food consumption. At study entry and every 8 months, patients had a whole-body dual-energy radiograph absorptiometry scan to determine lean and fat body mass.

Results: The analysis was based on >800 observations from 264 patients. Half of the participants had symptomatic major depressive disorder, 16% had depression that was in remission, and 34% had never experienced depression; nearly 30% had comorbid generalized anxiety disorder (GAD). Nearly half of the patients (n=127) were receiving an SSRI at study entry, and these patients were more likely than SSRI nonusers to be experiencing depression and to meet diagnostic criteria for generalized anxiety disorder.

Overall, participants' BMI z scores* did not change over the course of the study. However, changes in the BMI z score were inversely correlated with scores on the IDS and the BAI and positively correlated with the duration of exposure to SSRIs and the dosage (p<0.05 for all). Both lean and fat body mass increased on average over the study period. Both of these outcomes were positively associated with the duration and dosage of SSRI therapy, even after accounting for depression severity (p<0.03), which was negatively associated with these out-

comes. In a model that included both anxiety symptom severity and the SSRI dose, only the latter was associated with changes in fat and lean body mass. SSRI treatment was also associated, although not significantly, with an increase in visceral fat mass. The effect of duration of SSRI therapy on body mass index and fat body mass was larger in male than female subjects. SSRI therapy was also associated with less longitudinal growth, although the effect was small in this age group.

Most of the SSRI patients received citalopram, escitalopram, fluoxetine, or sertraline. In an analysis comparing the individual antidepressants, citalopram and escitalopram were associated with the largest increases in body composition measures compared with no treatment. Sertraline did not differ from no treatment, and the effects of fluoxetine were intermediate.

Calarge C, Mills J, Janz K, Burns T, et al: Body composition in adolescents during treatment with selective serotonin reuptake inhibitors. *Pediatrics* 2017; doi 10.1542/peds.2016-3943. From Baylor College of Medicine, Houston, TX; and other institutions. **Funded by the NIMH; and other sources. The authors declared no competing interests.**

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

*See Reference Guide.

Lurasidone for Adolescent Schizophrenia

In a manufacturer-sponsored, 6-week, placebo-controlled clinical trial, lurasidone (*Latuda*) was effective and well tolerated in adolescents with schizophrenia. The medication was associated with minimal changes in body weight, metabolic parameters, prolactin, and measurements of movement disorders.

Methods: The trial, conducted in 14 countries, enrolled 326 patients, aged 13–17 years, experiencing an acute exacerbation of schizophrenia. After tapering all psychotropic medications, participants received randomly assigned, fixed-dose lurasidone, 40 or 80 mg/day, or placebo. The primary efficacy outcome was change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score. Change in the Clinical Global Impression–Severity (CGI-S)* score was the key secondary outcome.

Results: Participants had a mean age of about 13 years at symptom onset, and 83% had received prior antipsychotic medication. Mean baseline PANSS total scores in the groups were 93–95, and the mean CGI-S was nearly 5.

Average change from baseline in the PANSS total score was greater with the 2 lurasidone doses than with placebo (effect size,* 0.51 for 40 mg and 0.48 for 80 mg lurasidone; see table). Both lurasidone doses showed significantly better efficacy than placebo on the PANSS total score beginning after the first week of treatment. More patients achieved response (i.e., $\geq 20\%$ decrease in PANSS total score) with lurasidone than placebo (number needed to treat,* 5 for both lurasidone doses). Rates of remission (i.e., CGI-S ≤ 3 on 8 selected PANSS symptoms) did not differ statistically from placebo. Patients who received lurasidone also showed greater improvement than the placebo group on measures of quality of life and global function.

Efficacy measures in adolescents with schizophrenia who received 6 weeks of lurasidone or placebo			
Outcome	40 mg/day Lurasidone	80 mg/day Lurasidone	Placebo
Mean PANSS total score at week 6	75.9 [†]	75.7 [†]	82.3
CGI-S	3.9 [†]	3.9 [†]	4.3
Responders at week 6	64% [†]	65% [†]	42%
Remission at week 6	36%	36%	30%

[†] p<0.001 vs placebo.

Rates of premature treatment discontinuation were 11% with 40 mg lurasidone, 9% with 80 mg lurasidone, and 18% with placebo. Withdrawal for adverse events was more frequent with placebo than active treatment; schizophrenia worsening was the most frequent adverse event leading to discontinuation. One patient receiving 40 mg/day lurasidone stopped medication because of suicidal ideation. Structured measures of akathisia and abnormal movements showed no significant difference among groups. Weight gain of $\geq 7\%$ occurred in 2–3% of the lurasidone groups and in about 5% of the placebo group. There were no clinically significant changes in the QTc interval and no deleterious effects on cognition. Adverse events did not differ between younger and older adolescents.

Discussion: Lurasidone is approved for treatment of schizophrenia in adults at dosages of 20–160 mg/day. In the present study, safety and tolerability were similar to that observed in adults. In addition, effect sizes for lurasidone were similar to those reported for other antipsychotics in adolescents, while cardiometabolic risk and prolactin changes appear to be smaller.

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

Goldman R, Loebel A, Cucchiari J, Deng L, et al: Efficacy and safety of lurasidone in adolescents with schizophrenia: a 6-week, randomized, placebo-controlled study. *Journal of Child and Adolescent Psychopharmacology* 2017; doi 10.1089/cap.2016.0189. From Sunovion Pharmaceuticals, Inc., Marlborough, MA; and other institutions. **Funded by Sunovion. All 5 study authors disclosed financial relationships with commercial sources, including Sunovion.**

*See Reference Guide.

Quetiapine vs Aripiprazole for First-Episode Psychosis

Aripiprazole and extended-release quetiapine had similar efficacy but differed substantially in adverse effects in an independently funded, head-to-head comparative trial in children and adolescents with first-episode psychosis. Both drugs had limited antipsychotic efficacy and a high level of adverse events.

Methods: The multicenter, investigator-initiated trial was conducted in Danish university pediatric and mental-health clinics. Participants were 113 in- or outpatients, aged 12–17 years, with first-episode psychosis and no or minimal previous exposure to antipsychotics. Patients were randomly assigned to receive aripiprazole, titrated to a maximum of 20 mg/day, or extended-release quetiapine, titrated to 600 mg/day. The primary efficacy outcome was change from baseline to week 12 in the positive symptom subscale of the Positive and Negative Syndrome Scale (PANSS). Key secondary outcomes were based on the drugs' expected adverse-effect profiles: change in body weight and homeostatic model assessment of insulin resistance (HOMA-IR), as well as standardized measures of akathisia and sedation. Response was defined as a $\geq 30\%$ reduction in the PANSS total score and a Clinical Global Impression–Improvement rating of much or very much improved. Remission was defined as a rating of mild or better on a group of PANSS items.

Results: Most of the 113 study participants had diagnoses within the schizophrenia/delusional disorder spectrum, with moderate-to-marked severity and a high level of psychosocial disability. Study dropouts were similar in the treatment groups: 35% of aripiprazole patients and 22% of the quetiapine group discontinued treatment before 12 weeks.

The mean reduction from baseline in the PANSS positive symptom score was 5.1 points with quetiapine and 6.2 with aripiprazole (effect size, * 0.002; $p=ns$). The response rate was 23% in both groups, and all but 1 patient with a response experienced remission.

Weight increased more rapidly with quetiapine than aripiprazole. At week 12, patients who received quetiapine had gained at least 7 lbs more than the aripiprazole group (effect size, 0.64; $p<0.0001$). HOMA-IR also increased to a greater degree with quetiapine (effect size, 0.35; $p=0.006$). Akathisia affected a larger proportion of the aripiprazole group at week 2

(60% vs 30%), but by week 12 the proportion was about 30% in both groups. Sedation was common throughout the study in both groups, affecting 72% of the quetiapine group and 92% of the aripiprazole group at week 12 ($p=0.01$).

Patients who received aripiprazole had more extrapyramidal symptoms, but metabolic outcomes (i.e., elevated levels of triglycerides, cholesterol, and prolactin) were worse with quetiapine. Patients who received quetiapine experienced improvement in cognitive performance over time, although this was limited to verbal fluency and symbol coding. Cognitive performance deteriorated in the aripiprazole group. Parent ratings of changes in executive function favored aripiprazole, however. Adverse effects were common with both agents, and fatigability, sedation, failing memory, depression, tension, increased sleep, tremor, akathisia, orthostatic dizziness, and weight gain affected >70% of patients overall.

Discussion: Results of this study suggest that clinicians should primarily base their antipsychotic choice between quetiapine and aripiprazole on adverse reactions. The 2 drugs did not differ in efficacy, and their effects on cognitive outcomes were mixed. Quetiapine might not be the drug of choice when cardiometabolic effects are a concern, while aripiprazole might be avoided in patients sensitive to neurological adverse reactions. The high rate of adverse effects seen with both agents indicates that rigorous adverse-event assessment is crucial in managing early-onset psychosis.

Pagsberg A, Jeppesen P, Klauber D, Jensen K, et al: Quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: the multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial. *Lancet Psychiatry* 2017; doi 10.1016/S2215-0366(17)30166-9. From the Child and Adolescent Mental Health Center, Capital Region of Denmark, Glostrup; and other institutions. **Funded by the National Research Council for Health and Disease Foundation for Health Promotion; and other sources. Six of 23 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names: aripiprazole—*Abilify*; quetiapine—*Seroquel*

*See Reference Guide.

Stimulant-Related Irritability

In children and adolescents with ADHD, methylphenidate-derived stimulants appear to be associated with reduced risk of irritability while amphetamine-derived stimulants appear to increase risk, according to findings of a meta-analysis.

Background: Significant irritability is present in up to 45% of children with ADHD. Stimulants have unclear effects on irritability according to clinical observation, but it is a commonly reported side effect.

Methods: The analysis was based on English-language reports of randomized controlled trials of any psychostimulant medication in children and adolescents with a diagnosis of ADHD or hyperkinetic disorder according to established criteria. Studies were required to have 7 days of on-treatment observation, the minimum for detecting changes in irritability symptoms. The primary outcome of the analysis was the proportion of patients in whom irritability was reported as an adverse effect of the medication. Clinician reports were relied on whenever available, but parent, teacher, or patient reports were used if necessary.

Results: Of 92 trials that otherwise met eligibility criteria, only 32 ($n=3664$) reported irritability as an adverse effect of stimulant medication. Taken together, the trials showed stimulants were associated with a 10% decrease in the risk of irritability relative to placebo. (See table, next page.) There was moderate heterogeneity among trials but no evidence of publication bias for reporting irritability. When stimulant classes were analyzed separately, methylphenidate derivatives were associated with reduced risk of irritability and amphetamine derivatives with increased risk. The difference between medication classes remained significant when the analysis was adjusted for the stimulant dose.

Risk of irritability with stimulant medication, relative to placebo		
	Relative Risk*	Significance
All psychostimulants	0.90	p=0.009
Methylphenidate derivatives	0.89	p=0.004
Amphetamine derivatives	2.90	p=0.01

No difference in the risk of irritability was found between short-acting and long-acting stimulants. Longer use of stimulants in trials was associated with a higher risk of irritability, relative to placebo, within the 1–8-week time frame of the trials. There was no significant association of irritability within either medication class with the age of patients, with trial design (crossover vs parallel-group), or with the identity of the rater as either a clinician or another adult observer.

Discussion: The difference between the 2 psychostimulant classes evaluated in the study may be explained by their differing mechanisms of action. It is also highly likely that because most of the trials included in the meta-analysis were industry-funded, irritability as a side effect was measured consistently within individual medications but differently between medications. The results of this analysis provide some guidance in selecting an initial ADHD medication. However, the difference between methylphenidate and placebo was small, and other medications might be preferable to treat irritability if it is the primary symptom.

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

Stuckelman Z, Mulqueen J, Ferracioli-Oda E, Cohen S, et al: Risk of irritability with psychostimulant treatment in children with ADHD: a meta-analysis. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.15r10601. From the Yale Child Study Center, New Haven, CT; and other institutions. **Funded by the NIH; and other sources. The authors declared no competing interests.**

Common Drug Trade Names: amphetamine derivatives—*Adderall, Vyvanse*; methylphenidate derivatives—*Ritalin, Concerta*

*See Reference Guide.

Reference Guide

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.

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.

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.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) 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.

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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Questions about Self-Assessment CME? We have the answers! See back page for details.

Triple-Bead Mixed Amphetamine Salts

A new once-daily triple-bead mixed amphetamine salts formulation (*Mydayis*) has received FDA approval for the treatment of ADHD in adults and adolescents aged ≥ 13 years. In clinical trials, the agent was shown to significantly improve symptoms beginning at 2–4 hours and lasting for up to 16 hours postdose. Common adverse effects were similar to those with other amphetamine formulations and included insomnia, decreased appetite, and weight loss in adults and adolescents; dry mouth, increased heart rate, and anxiety in adults; and irritability and nausea in adolescents. *Mydayis* is expected to become available in the U.S. later this year at strengths of 12.5, 25, 37.5, and 50 mg.

U.S. FDA approves Mydayis™ (mixed salts of a single-entity amphetamine product)—a new once-daily option for ADHD symptom control in patients 13 years and older [press release]. Lexington, MA; Shire PLC: June 20, 2017. Available at <https://www.shire.com/en/newsroom/2017/june/w6x937>.

Methylphenidate and Suicide Attempts

Results of a population-based longitudinal study, conducted to clarify the observed association between methylphenidate (*Ritalin*) and suicide, indicate that methylphenidate is not the cause of suicidal behavior.¹

Background: Results of a Swedish registry-based study comparing treated and untreated patients with ADHD found that methylphenidate or other stimulant use was associated with a >30% increase in the rate of suicide-related events,² raising concern about the association between stimulants and suicide. However, the analysis did not adjust for potential confounding factors, thus creating uncertainty about the association.

Methods: Data were analyzed from electronic medical records from the Hong Kong national database. Study subjects were all individuals aged 6–25 years who received ≥ 1 prescription for methylphenidate and who made a suicide attempt during the study period of 2001–2015. With each patient serving as his or her own control, rates of suicide attempts were compared for 4 risk windows: absence of methylphenidate (baseline period, including time before and after

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drug exposure); the 90 days before a first methylphenidate prescription; the first 90 days of methylphenidate use; and subsequent methylphenidate use. Patients remained in follow up until their 26th birthday, the end of the study period, a switch to another ADHD medication, or death. Patients who made a suicide attempt remained in follow-up.

Results: Of >25,000 patients given a prescription for methylphenidate during the study years, 154 made a suicide attempt. None of the attempts were fatal. Three-fourths of attempters were male, 73% had an ADHD diagnosis, and nearly half had a prescription for an antidepressant or antipsychotic during methylphenidate treatment. The median age at the time of a suicide attempt was 15 years.

Risk of a suicide attempt was highest in the 90 days preceding the methylphenidate prescription. (See table.) Risk remained elevated during the first 90 days of methylphenidate use before returning to near-baseline levels. Further analysis of the timing of attempts showed that the risk of suicide attempts increased significantly before the initiation of methylphenidate, reaching a peak within the 100 days before the start of treatment and subsiding throughout treatment. These relationships were consistent for both genders and all age groups.

Suicide attempts in relation to risk windows of methylphenidate use				
Risk window	Number of attempts	Incidence per 10,000 patient years	Adjusted incidence rate ratio*	Significance relative to pretreatment
Pretreatment–baseline	19	2.91	—	—
90 days before prescription	12	21.45	6.55	p<0.01
90 days after prescription	6	12.80	3.91	p<0.01
Later methylphenidate use	36	8.43	1.35	p=ns
After methylphenidate	81	11.80	—	—

Discussion: These observations indicate that the decision to start methylphenidate follows the period of increasing risk of suicide attempts, possibly reflecting changes in behavioral or mental health symptoms leading to a medical consultation. The decision to start methylphenidate may be in response to transient ADHD-related disorders or emerging problems such as depression or disruptive behavior disorder. While the results do not support a causal relationship between methylphenidate treatment and suicide, they also cannot be interpreted as showing that methylphenidate has an immediate effect in lowering suicide risk.

¹Man K, Coghil D, Chan E, Lau W, et al: Association of risk of suicide attempts with methylphenidate treatment. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.2183. From the University of Hong Kong; and other institutions. **Funded by the European Community's 7th Framework Programme; and other sources. Of 25 study authors, 14 disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

²Chen, Q, et al: Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study. *British Medical Journal* 2014;348:g3769.

*See Reference Guide.

GI Effects of Methylphenidate

According to a meta-analysis, methylphenidate (*Ritalin*) was associated with increased risks of decreased appetite, weight loss, and abdominal pain, but not other gastrointestinal adverse effects in children and adolescents with ADHD.

Methods: Randomized controlled trials of methylphenidate, either parallel-group or crossover, with a majority of participants aged <19 years, were identified from a recent Cochrane review.

Methylphenidate dosing forms could be either oral (immediate- or extended-release) or transdermal, and the control condition was either placebo or no treatment. Information on GI adverse events from the 61 trials (5983 patients) was ascertained using rating scales, spontaneous reports, or regular interviews by investigators.

Results: Methylphenidate was associated with a >3-fold increase in risk of reduced appetite in both parallel-group and crossover trials. The drug was also associated with decreased weight in parallel-group trials and with abdominal pain in the crossover studies. In neither of the analyses was methylphenidate associated with risk of diarrhea, dyspepsia, increased appetite, nausea, or vomiting. Risk of any GI adverse event did not differ according to the type of methylphenidate preparation, dosage, or duration of treatment.

Discussion: Guidelines for prescribing methylphenidate suggest that the risk of decreased appetite may be controlled by dosage reduction. The meta-analysis contradicts this advice, but the findings were based on only 10 studies, of generally low quality, comparing different dosages.

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

Holmskov M, Storebo O, Moreira-Maia C, Ramstad E, et al: Gastrointestinal adverse events during methylphenidate treatment of children and adolescents with attention deficit hyperactivity disorder: a systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *PLoS One* 2017; doi 10.1371/journal.pone.0178187. From Region Zealand Psychiatry, Slagelse, Denmark; and other institutions. **Funded by the Region Zealand Research Foundation. Two of the 12 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

*See Reference Guide.

CBT-Based Family Treatment for Suicide Prevention

Safe Alternatives for Teens and Youths (SAFETY), a cognitive behavioral therapy-based family treatment, had a protective effect against suicide attempts in adolescents in a preliminary, randomized, controlled trial. The treatment aims to strengthen protection and healthy connections within the family and to extended social ecological systems. It is 1 of very few evidence-based treatments for suicide-attempt prevention in adolescents.

Background: The SAFETY intervention is conducted by 2 therapists, mostly working separately (1 with the adolescent and 1 with a parent) over a 12-week span. The program includes an individualized treatment plan addressing the unique strengths of each youth and family; development of a SAFETY plan with concrete steps for safe coping; encouraging the parents to provide protective support, connectedness, and monitoring; practicing the SAFETY plan with parents present; and linkage to follow-up care. The program combines aspects of CBT, dialectical behavior therapy, and family-centered approaches.

Methods: Study participants were adolescents, aged 11–18 years, recruited from emergency departments, inpatient- or partial-hospitalization programs, outpatient services, or schools, who had a history of suicide attempt or nonsuicidal self-injury (NSSI) in the past 3 months and ≥3 lifetime episodes of self-harm. Youths were required to be in a stable family situation and to have a parent or caregiver willing to participate. Following screening, 42 adolescents (mean age, 15 years; 88% girls) were randomized to receive either the SAFETY intervention or enhanced treatment as usual (E-TAU), which consisted of a single in-clinic parent session, followed by multiple telephone contacts, with an emphasis on plans for protective monitoring and safety. The primary study outcome was the probability of a suicide attempt at the end of the 3-month treatment period.

Results: At study entry, 67% of participants had a recent emergency department visit or hospitalization. Half reported suicide attempts, and half reported only NSSI within the past 3 months.

They had a range of problems including major depressive disorder (55%) in the past year, problematic substance use (48%), and youth self-reported internalizing and externalizing behaviors (72% and 31%, respectively).

Participants in the SAFETY program received an average of 10 sessions and a maximum of 15. The E-TAU group received an average of 1.6 follow-up calls, and 82% were receiving treatment outside the study. During the 3-month treatment period, there were 6 suicide attempts in 4 young people, all in the E-TAU group. An additional 2 patients, 1 in each treatment group, prepared for but did not initiate an attempt; however, 1 of these, a SAFETY participant, made an attempt after 5 months. Overall, patients in the SAFETY program had a significantly reduced likelihood of a suicide attempt at 3 months ($p=0.01$; number needed to treat,* 3). Most of the difference was driven by the early part of the treatment period, and the effect of the SAFETY intervention weakened over time. Rates of NSSI during treatment were also lower in the SAFETY group ($n=8$), but the between-group difference was not significant.

Discussion: Integrated CBT is the only treatment with demonstrated efficacy in preventing suicide attempts in a randomized clinical trial. Both the SAFETY program and integrated CBT combine strong family and CBT interventions. Although adolescence is a time when peer interactions become more important, parents can still play key protective roles in suicide prevention. Because the positive effects waned over time, the protective value of the SAFETY program might be enhanced by including continuation or maintenance strategies.

Asarnow J, Hughes J, Babeva K, Sugar C: Cognitive-behavioral family treatment for suicide attempt prevention: a randomized controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 2017;56 (June):506–514. From the University of California, Los Angeles; and the University of Texas Southwestern Medical School, Dallas. **Funded by the NIMH; and the American Foundation for Suicide Prevention. Three of the 4 study authors disclosed relevant financial relationships with noncommercial sources; the remaining author declared no competing interests.**

*See Reference Guide.

Risk Calculator for Bipolar-Disorder Onset

An individual-level risk calculator for predicting onset of bipolar disorder has been developed using data from an ongoing longitudinal study of children and adolescents at familial risk.¹ The calculator predicts onset within the 5 years following an assessment with 76% accuracy.

Methods: Risk for conversion to bipolar disorder was evaluated in at-risk youth from the Pittsburgh Bipolar Offspring Study, which enrolled young people, aged 6–18 years, whose parents had bipolar I or II disorder, and community controls. Participants were evaluated every 2 years for the onset of bipolar disorder. The risk calculator was based on 7 predictive variables (see table) identified in a previous meta-analysis that did not include the Pittsburgh cohort. It is available online at <http://pediatricbipolar.pitt.edu/resources/risk-calculator>. The outcome of interest was the first time a participant met criteria for a manic, hypomanic, or mixed episode or bipolar disorder NOS.

Results: The study included 1058 visits in 412 offspring who were followed for a median of 9.5 years. Bipolar disorder developed in 54 participants (13%) at a median age of 14 years: bipolar I disorder ($n=9$), bipolar II disorder ($n=9$), and bipolar disorder NOS ($n=36$). The risk calculator discriminated between young people who did or did not convert to bipolar disorder with a 5-year area under the curve* of 0.76. The accuracy of risk prediction varied little under different test conditions,

Predictors included in risk calculator for bipolar spectrum disorder onset
Modified Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) Mania Rating Scale
Modified K-SADS Depression Rating Scale
Screen for Child Anxiety Related Emotional Disorders
Children's Affective Liability Scale
Children's Global Assessment Scale
Child age at visit
Parent age at onset of mood disorder

such as removing different variables or pairs of variables and excluding participants who had onset of bipolar disorder NOS. Parental age at onset was the only variable whose removal (in various combinations with others) uniformly decreased the accuracy of the prediction.

Discussion: This model provides clinically relevant discrimination between adolescents in whom bipolar spectrum disorders are/are not likely to develop within 5 years. Younger parental age at mood-disorder onset, the most important individual predictor within the model, is known to be associated with familial bipolar disorder.

Editorial.² While the risk calculator may be an important advance in the prediction of bipolar disorder, it is only relevant in a population at high familial risk in whom clinicians routinely evaluate anxiety and mood symptoms, and it should only be used with the guidance of an experienced clinician, and ideally only when the appropriate interventions are available.

¹Hafeman D, Merranko J, Goldstein T, Axelson D, et al: Assessment of a person-level risk calculator to predict new-onset bipolar spectrum disorder in youth at familial risk. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.1763. From the University of Pittsburgh, PA; and other institutions. **Funded by the NIMH. Seven of 14 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

²Mesman E, Hillegers M: A risk calculator for bipolar spectrum disorder in youth at familial risk [editorial]. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.1373. From the University Medical Center Utrecht; and Erasmus University Medical Center, Rotterdam, the Netherlands. **The author declared no competing interests.**

*See Reference Guide.

Long-Term Effects of Lisdexamfetamine

In a 2-year observational study, lisdexamfetamine dimesylate (*Vyvanse*) was associated with continued efficacy in children and adolescents with ADHD. Adverse effects were similar to those observed with shorter durations of treatment.

Methods: The study population of children and adolescents (aged 6–17 years) were either newly enrolled or continued from the manufacturer's earlier lisdexamfetamine studies. All had a primary diagnosis of ADHD, with baseline ADHD Rating Scale IV (ADHD-RS-IV) scores of ≥ 28 . All patients received open-label lisdexamfetamine, beginning with a 4-week dose-optimization phase and continuing for 100 weeks of maintenance. Dose adjustments could be made throughout the study. The primary objective of the study was to evaluate the long-term safety and tolerability of the drug. Patients were evaluated every 12 weeks after dose stabilization, and again 4 weeks after discontinuation.

Results: The analysis included 299 patients, of whom about 40% had participated in a previous lisdexamfetamine study. About 61% of patients completed all study visits. The mean lisdexamfetamine dosage was 50 mg/day, and the mean duration of exposure was 555 days. Adverse effects of lisdexamfetamine were common and reported by 90% of patients; most were mild (36%) or moderate (42%) and dose-related. The adverse-event profile was similar in children and adolescents.

During follow-up, there were 4 serious adverse events believed to be associated with treatment: 3 syncope events and 1 severe arrhythmia. One syncope event resulted in treatment discontinuation. The arrhythmia was related to a previously undiagnosed heart defect. Adverse events or lack of efficacy (which was inconsistently recorded as an adverse event) resulted in treatment discontinuation in 44 patients. The most common reasons for discontinuing were lack of efficacy (n=11) and decreased appetite or weight loss (n=9), with fewer patients discontinuing because of depressed mood, irritability, tics, insomnia, aggression, apathy, and tachycardia.

The authors identified several adverse events as being of special interest. Weight loss and decreased appetite affected 54% and 20% of patients, respectively. These peaked at weeks 1 and 12, respectively, and decreased thereafter. The lisdexamfetamine dose was adjusted because of

decreased appetite or weight loss in 15% and 18% of patients, respectively. Insomnia events were reported by 98 patients; 4 resulted in treatment discontinuation, and 17 patients still had insomnia at end of study. Headache affected 68 patients and was severe in 2. Psychiatric adverse events included 1 case of psychosis and mania, 3 instances of suicidal ideation or attempt, and 14 cases of aggression. The 1 suicide attempt was not judged to be drug related.

Lisdexamfetamine was associated with small increases in pulse rate and systolic and diastolic blood pressure. QTc prolongation was observed in 1 patient. There was a general shift to lower age-standardized height, weight, and body mass index during treatment.

Lisdexamfetamine continued to show clinical efficacy throughout the trial. ADHD-RS-IV scores decreased on average before stabilizing at week 48. About 80% of patients maintained Clinical Global Impression–Improvement (CGI-I)* ratings of much or very much improved. The rate of clinically relevant response ($\geq 30\%$ decrease in ADHD-RS and CGI-I score of 1 or 2) increased throughout early treatment, stabilizing at 77% at week 72.

Coghill D, Banaschewski T, Nagy P, Otero I, et al: Long-term safety and efficacy of lisdexamfetamine dimesylate in children and adolescents with ADHD: a phase IV, 2-year, open-label study in Europe. *CNS Drugs* 2017;31 (July):625–638. From the University of Melbourne, Australia; and other institutions. **Funded by Shire Development LLC. All 8 study authors disclosed financial relationships with commercial sources including Shire.**

*See Reference Guide.

Reference Guide

Area Under the Curve (AUC): A statistical measure of discrimination—i.e., the ability to correctly classify those with and without a disease. An AUC value of 1 represents perfect accuracy, while a value of 0.5 has accuracy that is no better than chance.

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.

Incidence Rate Ratio: The number of new cases of a condition in a defined (specified) group or population expressed as a ratio. For example, if there are 1000 people and a condition develops in 14 of them, the incidence rate is 14 per 1000 or 1.4%.

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.

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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Evening Methylphenidate

An investigational once-daily methylphenidate formulation taken in the evening provided extended coverage from the early morning hours throughout the day in a phase-III trial.

Background: HLD200 tablets consist of 2 microbead layers surrounding the methylphenidate core, with the outer layer providing predictably delayed release about 8–10 hours after ingestion and the inner layer providing controlled extended release throughout the following day. The formulation was designed to address the unmet need for treatment of ADHD-related functional impairment in the early morning, before the AM stimulant dose takes effect.

Methods: Study participants were children, aged 6–12 years, with a primary diagnosis of ADHD. Additional entry criteria included ADHD Rating Scale-IV (ADHD-RS-IV) scores at or above the 90th percentile for age and gender, Clinical Global Impression–Severity* (CGI-S) scores of ≥ 4 , difficulty performing a morning routine of ≥ 30 minutes between 6 AM and 9 AM, weight > 44 lbs, and at least partial response to methylphenidate. After a washout of prior medications, children were randomly assigned to receive HLD200 or placebo for 3 weeks. Study medication was taken at 8 PM initially; afterward, parents were allowed to vary the dosing time between 6:30 PM and 9:30 PM. HLD200 was initiated as a 40-mg dose and then increased to 80 mg if tolerated. The primary efficacy outcome was change from baseline in ADHD-RS-IV total score. As a secondary endpoint, ADHD-RS-IV scores were also obtained between 6 AM and 9 AM. Patient functioning was measured using the Before-School Functioning Questionnaire (BSFQ), which has a maximum score of 60, and the Parent Rating of Evening and Morning Behavior-Revised (PREMB-R PM and AM), which have maximum scores of 24 and 9, respectively.

Results: A total of 163 children were enrolled; 89% of the HLD200 group and 80% of the placebo group completed the study. Two-thirds were markedly ill at baseline, when the mean ADHD-RS-IV total score was 43. After 3 weeks of treatment, HLD200 was associated with a larger improvement in ADHD-RS-IV score than placebo (about 19 points vs 12 points; $p=0.002$).

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The active drug was superior to placebo beginning at the week-1 evaluation. HLD200 was also associated with greater early morning functional improvement at 3 weeks, measured with the BSFQ (about 25 points vs 16 points; $p < 0.001$), the PREMB-R AM (4.3 vs 2.2 points; $p < 0.001$), and PREMB-R PM (8 vs 4.3 points; $p = 0.002$).

One patient withdrew from active treatment because of an adverse event—mood swings. Sleep-related adverse effects were very common with both active treatment and placebo, but they were mostly mild and resolved with time, requiring a dosage reduction of the active drug in a small minority of patients. Appetite-related effects were mild or moderate and transient. Vital-sign changes were consistent with methylphenidate treatment.

Discussion: The short duration of the study and the inclusion of only school-aged children limit the generalizability of the results. However, if these limitations are addressed in future studies, HLD200 could fulfill an important unmet need in ADHD treatment: early morning efficacy that does not sacrifice later-day symptom control.

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

Pliszka S, Wilens T, Bostrom S, Arnold V, et al: Efficacy and safety of HLD200, delayed-release and extended-release methylphenidate, in children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (August):474–482. From the University of Texas Health Science Center at San Antonio; and other institutions. **Funded by Ironshore Pharmaceuticals & Development, Inc. All 11 study authors disclosed financial relationships with commercial sources, all but 1 with Ironshore Pharmaceuticals and Development.**

*See Reference Guide.

Problematic Social Media Use

Prevalence estimates of problematic social media use vary widely, in part because of diverse definitions and lack of a standardized measurement tool. In a population-based study, the Bergen Social Media Addiction Scale (BSMAS) was found to have appropriate psychometric properties and its use led to a prevalence estimate of 4.5% in a population of Hungarian adolescents. With cross-cultural validation, the BSMAS could be useful as a screening tool to identify those who would benefit from prevention or intervention programs.

Background: At present, there is no consensus definition of problematic social media use, or of any internet-related problems (other than DSM-5 internet gaming disorder). Due in part to this lack of consensus, prevalence estimates of problematic social media use in high school or college students range from about 3% to 47%. Excessive use of social media can impair academic performance and relationships and is correlated with depression and low self-esteem. According to the biopsychosocial theoretical model, problematic social media use can be determined by 6 addiction symptoms: mood modification, salience (i.e., total preoccupation), tolerance, withdrawal symptoms, interpersonal conflict, and relapse after a period of abstinence. This theoretical model informed the development of the BSMAS, a more general successor to the previously validated Bergen Facebook Addiction Scale.

Methods: The BSMAS rates the 6 items that comprise the biopsychosocial model of addiction on a 5-point scale, with each item scored between never and always. The scale was administered to a nationally representative sample of Hungarian adolescents in the 9th and 10th grades who were participating in an ongoing European school survey program assessing alcohol and drug use. The target population was 16 year olds, although it included a few students as old as the early 20s who were still in high school. Students were also assessed using Rosenberg's Self-Esteem Scale and the Center for Epidemiologic Studies Depression Scale. The sample, after excluding about 7% who did not use social media, consisted of nearly 6000 adolescents.

Results: Study participants used social media for an average of 23 hours per week (20.5 hours for boys, 25.7 hours for girls). Using a latent profile analysis* based on the 6 items of the BSMAS, the investigators identified 3 categories of social media use. The "no-risk" class comprised 78% of social media users and the "low-risk" group 17.2%. High-risk users made up 4.5% of all social media users, and were characterized by high scores on the withdrawal and tolerance items. Members of this group were more likely to be female, use the internet and social media for >30 hours per week, and have lower self-esteem and higher levels of depressive symptoms than other participants. Using a cutoff score of 19 as indicative of problematic use, the BSMAS had a sensitivity* of 83% for detecting individuals at high risk of developing problematic social media use and a specificity* of 99%.

Discussion: The at-risk group identified with the BSMAS was consistent in size with the more conservative prevalence estimates from other studies. Validity of the BSMAS is supported by its association with more hours of social media use, low self-esteem, and depressive symptoms. Within the at-risk group, the withdrawal component had the highest score, which suggests withdrawal symptoms should be targeted in prevention and treatment programs for problematic social media use.

Editor's Note: While the present report does not include a transcript of the BSMAS, the scale is based on a general rephrasing of the Bergen Facebook Addiction Scale, which is available at <http://smaddiction.web.unc.edu/bergen-facebook-addiction-scale>.

Banyai F, Zsila A, Kiraly O, Maraz A, et al: Problematic social media use: results from a large-scale nationally representative adolescent sample. *PLoS One* 2017; doi 10.1371/journal.pone.0169839. From Eotvos Lorand University, Budapest, Hungary; and other institutions. **Funded by the Hungarian National Research, Development and Innovation Office. The authors declared no competing interests.**

*See Reference Guide.

Tracking Behavior Problems with Neuroimaging

Internalizing and externalizing behavior problems were associated with altered brain development in a large, longitudinal, population-based study of children. The findings raise the possibility that emerging neuroimaging features of psychopathology may be the consequence of behavior problems, rather than the cause.

Methods: Study subjects (n=845) were participants, drawn from the general population, in an ongoing Dutch cohort study of maternal and child health. Behavioral symptoms were assessed with the Child Behavior Checklist (CBCL) when children were a mean age of 6 years and a second time at a mean age of nearly 10 years. Brain MRI scans were also obtained on 2 occasions, at mean ages of 8 and 10 years. Psychiatric outcomes were evaluated using the CBCL's internalizing and externalizing subscales and 4 DSM-oriented scales measuring affective, anxiety, ADHD, and oppositional defiant problems. MRI data included both global cortical macrostructure and white matter microstructure.

Results: At baseline, higher CBCL externalizing scores were associated with smaller total brain volume, cortical gray matter volume, white matter volume, and subcortical volume. Externalizing scores at age 6 years were associated with significantly smaller subcortical volumes at age 10 years, after adjusting for baseline values ($p < 0.01$). Internalizing scores were not associated with any macrostructural brain feature at baseline, but higher internalizing scores at age 6 years were associated with significantly smaller subcortical volume at age 10 ($p < 0.01$). Baseline macrostructural brain volumes were not associated with later scores for either type of behavior problem.

Neither externalizing nor internalizing scores at baseline were cross-sectionally associated with baseline white matter microstructure measures. Externalizing scores at the first assessment

were negatively associated with global fractional anisotropy (i.e., a diffusion tensor imaging biomarker of neuropathology and microstructural architecture) at the later assessment ($p < 0.01$), as were internalizing scores at the first assessment ($p < 0.01$). Baseline white matter measurements were not associated with later externalizing or internalizing problems. Baseline behavioral problems of either type were associated with smaller increases in individual white matter tracts at age 10 years. Among the individual DSM-oriented subscales, higher scores on affective, attention, and oppositional defiant scales at age 6 were associated with smaller increases in global fractional anisotropy.

Discussion: Most earlier structural neuroimaging studies of childhood disorders have been cross-sectional and based on case-control contrasts rather than dimensional measures of problems. Typically, subcortical structures and fractional anisotropy increase during late childhood. The present observations add to existing data suggesting that these trajectories may be modified by the presence of psychiatric symptoms at an early age. The findings suggest that, in addition to the standard model of the brain shaping behavior, behavior may also shape the brain.

Muetzel R, Blanken L, van der Ende J, El Marroun H, et al: Tracking brain development and dimensional psychiatric symptoms in children: a longitudinal population-based neuroimaging study. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.16070813. From Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands; and the NIH. **Funded by the Sophia Children's Hospital Research Foundation; and other sources. One study author disclosed a relevant financial relationship; the remaining 10 authors declared no competing interests.**

Adjunctive Celecoxib in Bipolar Disorder

In a small placebo-controlled trial, adjunctive celecoxib reduced symptoms of mania in adolescents with bipolar disorder.

Background: Celecoxib is an antiinflammatory drug that can curb levels of proinflammatory cytokines and prostaglandins that may contribute to the etiology of mania. Studies of adjunctive celecoxib in adults have found rates of remission that were higher and achieved at a faster pace in patients with bipolar mania, as well as rapid-onset antidepressant effects in patients experiencing depressive or mixed episodes.

Methods: Study subjects were 42 inpatients, aged 12–18 years (mean age, 15 years; 19 girls), with a DSM-IV diagnosis of bipolar disorder. Patients were required to have a Young Mania Rating Scale (YMRS) score of ≥ 20 , indicating moderate-to-severe mania. All patients received lithium, titrated to therapeutic blood levels; 3 mg/day risperidone; and double-blind, randomly assigned adjunctive placebo or 100 mg celecoxib b.i.d. The primary outcome measure was change in YMRS score after 8 weeks of treatment.

Results: Of the 42 randomized patients, 1 in each group withdrew consent during the first week; and the remaining 40 were included in the final analysis. All completed the trial and participated in follow-up. During treatment, all but 6 patients (2 in the celecoxib group, 4 in the placebo group) were discharged from the hospital.

The mean baseline YMRS score was 37 in both treatment groups. At week 8, scores had decreased by 28 points in the celecoxib group and by 24 points in the placebo group (mean difference 3.85; $p = 0.04$; effect size, $^* 0.68$). Differences in response and remission rates favored celecoxib but did not reach significance compared with placebo. Response, when defined as a Clinical Global Impression–Improvement* score ≤ 2 , occurred in 95% and 70% of the celecoxib and placebo groups, respectively; when defined as a $\geq 50\%$ decrease in YMRS total score, response occurred in 100% and 90%, respectively. Remission (i.e., final YMRS score of ≤ 12) occurred in 85% of the celecoxib group and 60% of the placebo group. The frequency of commonly reported adverse events (e.g., abdominal pain, tremor, increased

appetite, dry mouth) did not differ between the 2 groups. No serious adverse events were reported, and no deaths occurred.

Discussion: Celecoxib, long available to treat juvenile rheumatoid arthritis, has known cardiovascular risks. However, no cardiac events were observed in this study, possibly because of the small sample size or short treatment duration. Some studies have shown elevated inflammatory cytokines and tumor necrosis factor in patients with bipolar disorder, and lithium and antipsychotics can restore inflammatory homeostasis. Larger, more stringently designed studies with longer-term follow-up are needed.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial, but the source of funding was not included in the report.

Mousavi S, Khezri R, Karkhaneh-Yousefi M-A, Mohammadinejad P, et al: A randomized, double-blind placebo-controlled trial on effectiveness and safety of celecoxib adjunctive therapy in adolescents with acute bipolar mania. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (August):494–500. From Tehran University of Medical Sciences, Iran. **Source of funding not stated. The authors declared no competing interests.**

Common Drug Trade Names: celecoxib—*Celebrex*; risperidone—*Risperdal*

*See Reference Guide.

Oxytocin for Social Deficits in Autism

In a placebo-controlled trial, beneficial effects of intranasal oxytocin (*Syntocinon Nasal Spray*; not available in the U.S.) on social deficits in children with autism were linked with initially low oxytocin levels. This result may explain the conflicting findings of previous oxytocin trials.

Background: Single-dose studies have generally shown positive effects of oxytocin on social information processing, emotion recognition, and social learning. However, treatment trials in autism spectrum disorders have had mixed results. Many trials have shown significant variability in response, which suggests biomarkers might help identify those more likely to benefit.

Methods: The study participants (n=32; 27 boys) were aged 6–12 years and met DSM-IV-TR or DSM-5 criteria for autism of at least moderate severity. Concomitant medications (e.g., SSRIs, antipsychotics, benzodiazepines, stimulants) were required to be stable for ≥4 weeks before study entry. Treatment consisted of randomly-assigned, double-blind oxytocin (48 IU/day) or placebo nasal spray, supplied to parents at the beginning of the study and administered twice daily for 4 weeks. At baseline and after 4 weeks, blood samples were assayed for levels of plasma oxytocin and gene expression for the 2 receptors primarily involved in the prosocial effects of oxytocin, OXTR and V1AR. The primary efficacy outcome was improvement in social abilities, measured with the Social Responsiveness Scale (SRS).

Results: Mean baseline SRS total scores were 107 in the oxytocin group and 106 in the placebo group. After 4 weeks of treatment, scores decreased by a significantly larger margin with oxytocin than with placebo (about 10 points vs 3 points; $p=0.02$). Pretreatment oxytocin levels were significantly associated with improvements in SRS score; patients with the lowest pretreatment levels experienced the greatest improvements in social ability with oxytocin treatment ($p=0.002$). Unexpectedly, pretreatment oxytocin levels predicted response to placebo as well, possibly suggesting that increased secretion of endogenous oxytocin, perhaps associated with enhanced social interactions during the trial, could accompany improvement in social behavior in children with initially low oxytocin levels. Compared with placebo, oxytocin treatment did not affect the secondary outcomes of repetitive behaviors and anxiety. Treatment was well tolerated, with no serious adverse effects reported.

Discussion: While these study results suggest that oxytocin treatment may improve social abilities in patients with autism spectrum disorders, particularly those with low pretreatment oxytocin levels, larger, more stringent studies are needed to replicate the findings.

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

Parker K, Oztan O, Libove R, Sumiyoshi R, et al: Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism. *Proceedings of the National Academy of Sciences* 2017;114 (July 25):8119–8124. From Stanford University, CA. **Funded by the Mosbacher Family Fund for Autism Research; and other sources. The authors declared no competing interests.**

*See Reference Guide.

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.

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.

Latent Profile Analysis: A mixture modeling statistical technique used to identify groups of people according to their responses to certain continuous variables. Individuals with similar responses are classified in the same group.

Sensitivity and Specificity: Statistical measures of the performance of binary classification tests. Sensitivity measures the proportion of actual positives that are correctly identified (i.e., the percentage of sick people who are correctly identified as having the condition). Specificity 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). A perfect predictor would have 100% sensitivity and specificity.

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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Azithromycin for Acute-Onset OCD

In a placebo-controlled pilot study, azithromycin (*Zithromax*) reduced the severity of obsessive-compulsive symptoms in children with recent-onset, severe OCD possibly triggered by an infection. This preliminary result is consistent with those of other recent, small studies of various antibiotics for neuropsychiatric symptoms in childhood.

Methods: Study participants (n=31) were aged 4–14 years and met criteria for new-onset or relapse of pediatric acute-onset neuropsychiatric syndrome (PANS), with or without a recent group A streptococcal infection (PANDAS). For study inclusion, they were required to be experiencing abrupt or dramatic onset OCD symptoms of at least moderate severity (Children’s Yale-Brown Obsessive Compulsive Scale [CY-BOCS] total score of ≥ 16 and Clinical Global Impression–Severity* [CGI-S] score of ≥ 4), as well as ≥ 2 additional neuropsychiatric symptoms such as anxiety, tics, or frequent urination. Because of the difficulty of confirming a recent infection for each OCD episode, study patients were enrolled irrespective of whether they met criteria for PANS. Participants were randomly assigned to 4 weeks of double-blind treatment with either 10 mg/kg/day azithromycin (maximum dosage, 500 mg/day) or placebo. All children received a probiotic to prevent antibiotic-associated diarrhea. The primary outcome measures were the CY-BOCS and the CGI-S.

Results: Of the 31 enrolled children, 24 were receiving medication at baseline including allergy medicines (n=9) and SSRIs prescribed for OCD symptoms (n=3). A total of 19 children had a recent group A streptococcal infection identified as a trigger or associated with the current OCD episode, and 13 had a recent upper respiratory infection. OCD symptoms were present for an average of nearly 10 weeks before study enrollment.

Azithromycin was associated with a larger reduction in the average CGI-S score than placebo: mean scores at week 4 were 4.06 for azithromycin and 4.93 for placebo ($p=0.003$; effect size,* 1.61). Children receiving azithromycin had a 22% decrease in score, compared with a 1% decrease in the placebo group ($p=0.008$), with 7 and 1, respectively, meeting criteria for

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response (41% vs 7%; $p=0.045$). Although numeric differences in CY-BOCS improvement favored azithromycin (30.5% decrease vs 17%; effect size, 0.79), between-group differences were not significant. The number of treatment responders, when defined as a $\geq 30\%$ reduction in the CY-BOCS score, also did not differ significantly between the groups: 8 vs 3 with azithromycin and placebo, respectively (47% vs 21%). The groups did not differ in change from baseline in tic severity, cognitive function, or mood. Patients with a higher level of tic severity at baseline were more likely to have experienced symptomatic response with azithromycin treatment. No other clinical features, including OCD-onset characteristics or the presence of an infectious trigger, distinguished children more likely to have response to the antibiotic.

Discussion: These results suggest antibiotic treatment may reduce rapid-onset OCD symptom severity, particularly in children with moderate-to-severe tics. The efficacy of this treatment was partially obscured by the high rate of placebo response, which may be partially attributable to the intermittent course of OCD in children or to the effects of probiotic treatment.

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

Murphy T, Brennan E, Johnco C, Parker-Athill E, et al: A double-blind randomized placebo-controlled pilot study of azithromycin in youth with acute-onset obsessive-compulsive disorder. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (September):640–651. From the University of South Florida, St Petersburg; and other institutions. Funded by Massachusetts General Hospital. Three of 7 study authors disclosed relevant financial relationships; the remaining authors declared no competing interests.

*See Reference Guide.

Predictors of Internalizing Problems

Early risk factors, some appearing before school entry, were associated with later escalation of internalizing problems in a longitudinal study of school-aged children.

Methods: The analysis was conducted as part of a larger cohort study of Australian children, assessed first at age 4–5 years and then every 2 years thereafter. The analysis included 3153 children with complete, mother-reported data on internalizing problems in the 4 study waves (i.e., ages 4–5 years, 6–7 years, 8–9 years, and 10–11 years). Internalizing problems in the 3 later waves were measured with the Emotional Symptoms subscale of the Strengths and Difficulties Questionnaire (SDQ). The investigators also measured child emotional dysregulation, externalizing problems, teacher-reported peer relations, parenting behaviors, socioeconomic status, and maternal mental health. The analysis was designed to develop models predictive of both the initial prevalence of internalizing problems and the growth trajectory of the problems over the 3 older age waves.

Results: Internalizing problems were more likely to occur in girls and in children who at age 6–7 years had greater emotional dysregulation and externalizing problems and who had a mother who reported poorer mental health and a more angry parenting style. In addition, poorer maternal mental health and peer problems in 4–5 year olds were associated with more internalizing problems 2 years later. The growth rate of internalizing problems was increased in girls and in children with higher levels of emotional dysregulation and peer problems at age 6–7 years. Growth was also increased in children who, at age 4–5 years, had higher externalizing problems and peer problems and mothers with poorer mental health. Socioeconomic status was not associated with the initial prevalence or with the growth of internalizing problems.

Discussion: Childhood internalizing problems are subject to change, making them potential targets for early intervention. Emotional dysregulation at age 4–5 years may not be as relevant as later dysregulation because many children acquire the ability to regulate themselves when they enter school. Early but not later externalizing problems were strongly predictive of the growth in internalizing problems, perhaps because externalizing problems tend to be stable

over childhood, contributing to greater difficulties and a negative self-image. The study results support the recognized importance of peer interactions and maternal mental health. Attention to social and emotional skill development in children transitioning to school and programs to support maternal mental health could be useful in preventing later internalizing problems.

Wang C, Williams K, Shahaeian A, Harrison L: Early predictors of escalating internalizing problems across middle childhood. *School Psychology Quarterly* 2017; doi 10.1037/spq0000218. From Charles Sturt University, Bathurst, Australia; and other institutions. **Funded by the Australian Government's Collaborative Research Networks programs. The authors did not include disclosure of potential conflicts of interest.**

ADHD Medications and Substance Use Problems

In a longitudinal study that compared within-patient experience, treatment with stimulants or atomoxetine (*Strattera*) was associated with lowered risk of substance use problems.¹

Background: ADHD is associated with increased risk of co-occurring substance use disorders. Many disorder-specific characteristics, including the propensity toward impulsive risk-taking behavior, co-occurrence of mental health and behavioral problems, psychosocial risk factors, and self-treatment of symptoms, likely underlie the association. Concerns have also been raised that stimulant use could sensitize patients with ADHD to the rewarding effects of drugs, thus leading to increased risk of substance use disorders. However, it is also possible that by reducing the ADHD symptoms and impairments, stimulant and other medications may decrease risk for substance use disorder.²

Methods: The study cohort was drawn from a large U.S. commercial insurance database. Nearly 3-million enrollees with a diagnosis of ADHD or a prescription for a stimulant or atomoxetine were identified. Atomoxetine was the only non-stimulant included because others are often used as adjunctive or secondary treatments. The analysis excluded individuals aged ≤13 years as well as time periods when individuals did not have prescription coverage. Substance-related events were defined as any emergency department claims with a non-tobacco substance use disorder diagnosis. The investigators conducted 3 analyses: substance-related events in ADHD patients versus matched controls without an ADHD diagnosis; substance-related events in patients with ADHD while on medication versus off medication; and long-term within-individual associations after 2 years.

Results: Associations between ADHD medication and substance-related events differed in men (53% of the ADHD cohort) and women and were analyzed separately. Both male participants (median age, 21 years at the start of follow-up) and female participants (median age, 28 years) with ADHD were more likely than those without ADHD to have a substance-related event. (See table.) In within-individual models that excluded potentially confounding individual-level factors, ADHD medication was associated with a 35% lower risk of substance-related events in men and a 31% lower risk in women. These associations were consistent in subsets of individuals with and without a prior substance use disorder diagnosis, regardless of concurrent psychotropic medication or psychotherapy, and in those experiencing a first substance-related event. The 2-year analysis showed minor increases in risk of substance-related events in both genders, but the overall reduction in risk persisted.

Concurrent and longitudinal associations between ADHD medication and substance-related events	
	Adjusted odds ratio*
Male patients	
ADHD vs non-ADHD patients	2.69
Within-individual on vs off medication	0.65
Long-term within-individual	0.81
Female patients	
ADHD vs non-ADHD patients	3.30
Within-individual on vs off medication	0.69
Long-term within-individual	0.86

Discussion: Accumulating evidence suggests that ADHD medication may protect against not only substance use problems, but related outcomes such as injuries, accidents, criminality, depression, and suicide. In the short term, medications may reduce impulsive decision making. Long-term effects may be the result of changes in habitual behaviors and decisions, but appear to weaken somewhat.

¹Quinn P, Chang Z, Hur K, Gibbons R, et al: ADHD medication and substance-related problems. *American Journal of Psychiatry* 2017;174 (September):877–885. From Indiana University, Bloomington; and other institutions. **Funded by the NIMH; and other sources. Three of 10 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

²Asherson P: Drug treatments for ADHD reduce risk of substance use disorders [editorial]. *American Journal of Psychiatry* 2017;174 (September):827–828. From King's College London, U.K. **The author disclosed financial relationships with commercial sources.**

*See Reference Guide.

Anxiety Disorder Treatments

Cognitive behavioral therapy (CBT) and SSRIs are effective in treating anxiety symptoms in children and adolescents, according to a systematic review and meta-analysis of all currently recommended treatments.¹ SNRIs are also effective, although supported by a smaller evidence base. All of the treatments are safe and well tolerated.

Methods: The meta-analysis included controlled trials and observational studies from a wide scope of sources. Anxiety disorders were examined as a class, excluding only obsessive-compulsive disorder and posttraumatic stress disorder, which are typically treated differently from the other disorders in the class. The analysis included studies of patients, aged 3–18 years, who received CBT, medication, or both. Comparison groups could receive another active treatment, placebo, wait-listing, observation alone, or treatment as usual. In the included studies, CBT consisted of some combination of cognitive restructuring, relaxation training, and exposure therapy and was limited to individual face-to-face sessions with the child, with varying degrees of parent involvement. Non-comparative studies were included if they provided information about adverse events. The primary outcomes of interest were anxiety symptoms, treatment response (loss of principal anxiety diagnosis or Clinical Global Impression (CGI)–Severity* [CGI-S] score of 1 or 2), remission (loss of all anxiety diagnoses or CGI–Improvement* score of 1 or 2), and adverse events.

Results: The analysis included 115 studies with a total of >7700 patients. Participants had a mean age of 9 years, and 56% were girls. A total of 40% of studies included children with comorbid non-anxiety disorders. The medications studied were SSRIs, SNRIs, tricyclic antidepressants, and benzodiazepines. Outcomes were compared separately for clinician-, parent-, and child-reported outcomes and for the different control treatments.

SSRIs were significantly superior to placebo for all outcomes, with effect sizes* of 0.42 for child-rated measures, 0.61 for parent-rated measures, and 0.65 for clinician-rated measures. Relative risks* for response and remission with SSRIs were 1.96 and 2.04, respectively. SNRIs were also significantly superior to placebo, but only for clinician-rated measures (effect size, 0.45). No evidence supported the use of tricyclics or benzodiazepines.

CBT was compared with pill placebo, active medications, and various other control conditions for the 3 different types of informant. Results of these comparisons were generally positive, favoring CBT with effect sizes ranging from 0.36 to 1.36. Only 2 studies compared the CBT–medication combination with either treatment alone, both supporting the combination. There were only 2 head-to-head drug comparisons, neither finding a clear advantage for either medication. In a network meta-analysis,* CBT performed as well as any individual medication and all medications pooled.

A total of 82 studies reported adverse events. No serious adverse events were reported for any medication. Of 3 studies with data on suicidality or self-harm, only 1 identified suicidal ideation, in 3 patients receiving venlafaxine (*Effexor*). Studies were too small or too short to assess suicidality with SSRIs or SNRIs.

Editorial.² The summarized evidence suggests that multiple treatments can improve anxiety symptoms substantially. However, there are minimal data on the comparative efficacy of different drugs, and the best-researched drugs are off label for childhood anxiety disorders. In addition, acute treatment is not expected to result in full remission for many children, even those receiving gold-standard therapy.

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

¹Wang Z, Whiteside S, Sim L, Farah W, et al: Comparative effectiveness and safety of cognitive behavioral therapy and pharmacotherapy for childhood anxiety disorders. *JAMA Pediatrics* 2017; doi 10.1001/jamapediatrics.2017.3036. From the Mayo Clinic, Rochester, MN. **Funded by the Agency for Healthcare Research and Quality. One study author disclosed a financial relationship with a commercial source; the remaining 17 authors declared no competing interests.**

²Asarnow J, Rozenman M, Carlson G: Medication and cognitive behavioral therapy for pediatric anxiety disorders: no need for anxiety in treating anxiety [editorial]. *JAMA Pediatrics* 2017; doi 10.1001/jamapediatrics.2017.3017. From the University of California, Los Angeles; and the State University of New York at Stony Brook. **The authors declared no financial relationships with commercial sources.**

*See Reference Guide.

Antidepressant Efficacy in Common Pediatric Disorders

According to the results of a systematic review and meta-analysis, SSRIs and SNRIs are superior to placebo in children and adolescents with common psychiatric disorders, but not by a large margin.¹

Methods: This review assessed the efficacy of second-generation antidepressants—SSRIs and SNRIs—in children and adolescents with depressive disorder, anxiety disorders, obsessive-compulsive disorder (OCD), or posttraumatic stress disorder (PTSD). The analysis included placebo-controlled clinical trials of medication, with or without accompanying psychosocial interventions, in patients aged <18 years. The primary outcomes were those reported by each study, using a standardized, dimensional symptom scale specific to the disorder in question or a general severity scale.

Results: The analysis included 36 trials with a total of 6778 participants. There were 17 trials in depressive disorders, 10 in anxiety disorders, 8 in OCD, and 1 in PTSD. The combined analysis found small drug–placebo difference (see table) that favored active treatment. Medication effects were stronger in anxiety disorders and OCD than in depression, largely because the placebo effects in depression were large. In the comparison between drug categories, SSRIs were superior to SNRIs in anxiety disorders, but not in depressive disorders. No studies investigated SNRIs in OCD or PTSD.

Patients taking antidepressants reported more serious adverse events and treatment-emergent adverse events than those taking placebo. Discontinuation for an adverse event was significantly more common with an antidepressant than placebo (relative risk,* 1.79; p<0.001). Rates of adverse events did not differ between SSRIs and SNRIs.

Drug–placebo differences for SSRIs and SNRIs combined in common pediatric psychiatric disorders		
	Effect Size*	Significance
All disorders	0.32	p<0.001
Depressive disorders	0.20	p<0.001
Anxiety disorders	0.56	p<0.001
OCD (SSRIs only)	0.39	p<0.001
PTSD (SSRIs only)	0.16	p=ns

Editorial.² These observations indicate pharmacotherapy offers similar efficacy to that reported for psychological interventions in common pediatric psychological problems, and both fall short of the ideal. Given the potential for harm from medication, psychotherapy may be a preferred first option. Patients who present with these problems may also benefit from simple strategies such as attention and support, education, relaxation, mindfulness, and lifestyle changes. The large placebo effect in depression suggests that in young people, access to care, attention, and support can result in improvement of symptoms.

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

¹Locher C, Koechlin H, Zion S, Werner C, et al: Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: a systematic review and meta-analysis. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.2432. From the University of Basel, Switzerland; and other institutions. **Funded by the National Library of Medicine; and other sources. One study author disclosed financial relationships with commercial sources; the remaining 7 authors declared no competing interests.**

²Merry S, Hetrick S, Stasiak K: Effectiveness and safety of antidepressants for children and adolescents: implications for clinical practice [editorial]. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.2410. From the University of Auckland, New Zealand; and the University of Melbourne, Australia. **Two authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

*See Reference Guide.

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.

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.

Network Meta-Analysis: A study design 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 or more 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.

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.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) 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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Supplement for Self-Injurious Behavior

In a pilot study, *N*-acetylcysteine (NAC), an over-the-counter supplement with neuroprotective activity in the brain, showed promise in reducing nonsuicidal self-injury (NSSI) in a group of adolescents and young adults.

Methods: Study participants, recruited from the general public and by clinical referrals, were aged 13–21 years and had a history of ≥ 4 lifetime episodes of NSSI, including an episode within a month of study entry. The diagnosis of NSSI was confirmed using structured interviews, including both patient and parent interviews in those under age 18 years. Levels of NSSI were measured using the self-report Inventory of Statements About Self-Injury–Lifetime version (ISAS) and the clinician-administered Deliberate Self-Harm Inventory (DSHI). All participants received treatment for 8 weeks with open-label NAC, initiated at 600 mg b.i.d. and gradually increased to 1800 mg b.i.d. after week 4. The primary outcome was the number of NSSI episodes since the previous visit, based on a consensus of ISAS and DSHI scores.

Results: The trial enrolled 36 patients, of whom 25 completed the final study visit. The single male participant was not included in the outcome analysis. Participants had high rates of depression and anxiety (71% and 94%, respectively); 15 were taking medications; and 9 had a history of suicide attempts.

Over the 8 study weeks, the mean weekly frequency of NSSI episodes decreased from 0.74 to 0.35 ($p=0.022$ after correction for multiple comparisons). Those with greater lifetime severity of NSSI were more likely to show a response ($p=0.019$). Demographic factors and other baseline clinical factors were not predictive of response. In addition to changes in NSSI frequency, patients had significant reductions from baseline in average scores on the Beck Depression Inventory, from about 32 to 24 points ($p<0.0001$). Improvements in NSSI were not correlated with changes in the BDI. Patients also showed declines in multiple subscales of the Symptom Checklist-90: anxiety, depression, hostility, obsessive-compulsive, phobic anxiety, psychoticism, interpersonal sensitivity, somatization, and paranoid ideation.

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Discussion: Available treatment options for NSSI are very limited. If the present findings are replicated, NAC supplementation may be an option for patients who lack access to the intensive psychological therapies available, or to augment these therapies. NAC is a precursor to glutathione, the primary antioxidant in the brain. It also may modulate the glutamate transporter, an action that may alleviate addictive behaviors. While both NSSI and depression improved with NAC treatment in this study, analysis revealed that the changes were not correlated, suggesting that the effects may be independent.

Cullen K, Klimes-Dougan B, Schreiner M, Carstedt P, et al: *N-acetylcysteine for nonsuicidal self-injurious behavior in adolescents: an open-label pilot study. Journal of Child and Adolescent Psychopharmacology* 2017; doi 10.1089/cap.2017.0032. From the University of Minnesota, Minneapolis. **Funded by the University; and the NIMH. The authors declared no competing interests.**

Plasma Lipid Biomarkers for Psychotic Disorder

Children who had onset of a psychotic disorder by age 18 years were found to have lipidomic alterations at age 11 years, suggesting a possible early biomarker signature for psychosis. The alterations were indicative of inflammation and altered phospholipid metabolism, consistent with what is believed to be the pathophysiology of schizophrenia.

Methods: Study participants were enrollees in the Avon Longitudinal Study of Parents and Children, an ongoing study of a general-population cohort of >14,000 children and their families. Psychotic experiences were assessed at ages 11 and 18 years using the Psychosis-Like Symptoms interview. A total of 38 individuals with psychotic disorder at age 18 years had plasma samples available from age 11 years, 25 of whom also had samples drawn at age 18 years. Subjects were matched for age and body mass index to randomly selected controls who did not have psychosis or psychosis-like symptoms. Differences in lipid and metabolite levels were compared between the psychosis and control groups at both ages.

Results: At age 11 years, levels of 32 lipids differed significantly ($p < 0.05$) between children who went on to have a psychotic disorder and those who did not. Of these, 8 remained significantly elevated after statistical correction for multiple comparisons. In contrast, levels of 23 lipids differed significantly ($p < 0.05$) between 18 year olds with a psychotic disorder and those without; all but 1 were decreased. None of the lipids survived correction for multiple comparisons in the 18 year olds.

Discussion: Elevated lipids found in this study have been associated with inflammatory effects involved in the pathogenesis of many diseases, including atherosclerosis and diabetes. The finding of lipids that were elevated at age 11 and decreased at age 18 suggests that biomarker profiles may change with age and that the pathophysiological process can alter over time and with proximity to disease onset.

O'Gorman A, Suvitaival T, Ahonen L, Cannon M, et al: Identification of a plasma signature of psychotic disorder in children and adolescents from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. *Translational Psychiatry* 2017; doi 10.1038/tp.2017.211. From the Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin; and other institutions. **Funded by the UK Medical Research Council; and other sources. The authors declared no competing interests.**

Parental Diversion of ADHD Medications

Household diversion of stimulants was reported by 1 in 6 parents of children with ADHD who completed an anonymous survey. This preliminary study suggests that diversion is not limited to the better-recognized phenomenon of peer diversion among adolescents and young adults.

Methods: A convenience sample of parents attending community-based educational presentations on ADHD were offered the survey, which was developed for the study. Respondents were parents of children, adolescents, and young adults currently taking stimulant medications. The questionnaire assessed demographics, household stress levels, and medication

storage and access, as well as the occurrence of diversion. In addition, to gauge media influence, respondents were asked if they had seen an episode of a specific television series that depicted parental diversion of stimulants.

Results: A total of 180 parents from 164 households completed the survey. Nearly 30% of parents reported storing their child's medication in plain sight, 42% kept it out of sight but available to anyone in the house, 24% kept it hidden but not locked, and only 3% kept it locked up.

A total of 28 parents (16%) reported household diversion of stimulant medications, most commonly taken by the responding parent or another adult, but occasionally given by an adult to another child in the household. Another 24 parents (13%) reported being tempted to take their child's stimulant, usually on isolated occasions, under stressful circumstances.

About half of all parents reported that they either had a diagnosis of ADHD themselves or suspected that they had it. Those with diagnosed or suspected ADHD were more than twice as likely as others to self-administer their child's stimulants or to be tempted to do so (33% vs 17%; $p=0.01$). Of those who self-administered, 9 reported they were self-medicating their own ADHD and 4 were trying to see if they could get high. Less common reasons for taking their child's medication were the need to get work done, wanting to try the medication on themselves before giving it to the child, and concern about side effects.

Nearly 40% of adults had seen the TV series episode featuring medication diversion. These adults were more likely than others to self-administer stimulants or to be tempted, even though half agreed that the episode trivialized the danger of stimulants. Diversion was not associated with household stress levels or with the parent's gender, ethnicity, age, or educational level.

Discussion: Peer diversion of prescription stimulants among adolescents and young adults has received a considerable amount of study; however, household diversion, which has not previously been studied, also appears to be a significant issue. Clinicians should be aware that adults may be motivated to self-medicate for their own diagnosed or suspected ADHD. It should be noted that although the newer long-acting stimulants are marketed as being less prone to abuse than short-acting agents, at least half of the parents in this study who self-administered used a long-acting formulation.

Pham T, Milanaik R, Kaplan A, Papaioannou H, et al: Household diversion of prescription stimulants: medication misuse by parents of children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (October):741–746. From Steven and Alexandra Cohen Children's Medical Center of New York, Lake Success. **Source of funding not stated. The authors declared no competing interests.**

Antidepressants and Diabetes Onset

Use of SSRI, SNRI, and tricyclic antidepressants was associated with increased risk of type 2 diabetes in a population-based study of children and adolescents. Risk was intensified with higher cumulative antidepressant doses and longer duration of use.

Methods: The study was based on a Medicaid database covering 4 large, geographically diverse states. The study cohort comprised individuals, aged 5–20 years, who received an initial prescription for an antidepressant in 2005–2009. Onset of type 2 diabetes was compared between current and former antidepressant users (rather than non-users, who are less similar to current users). Patients with polycystic ovary syndrome and those who were pregnant were excluded. Type 2 diabetes was identified by an inpatient stay or outpatient care with a diabetes diagnosis or the prescription of antidiabetic medication, excluding young people who were prescribed only insulin (indicating type 1 diabetes).

Results: Nearly 120,000 young people who had started an antidepressant were identified, most were aged 10–17 years. Antidepressants were prescribed for depression in 37%, ADHD in 26%,

and anxiety disorders in 18%. During a mean of nearly 2 years of follow-up, there were 233 incident cases of type 2 diabetes. Compared with former use of antidepressants, current use was associated with a nearly 2-fold increase in diabetes risk. (See table.) Risk was increased with current use of SSRIs, SNRIs, and tricyclics, but not with other antidepressants.

Risk of type 2 diabetes intensified with increasing duration of SSRI or SNRI use, reaching a maximum with >210 days of use (relative risk,* 2.66 compared with 1–90 days of use). Risk was increased by a similar amount in young people who had received the highest cumulative SSRI/SNRI dose. Neither cumulative dose nor duration of use affected diabetes risk with other antidepressants.

Adjusted relative risk for type 2 diabetes with current antidepressant use, compared with former use	
	Adjusted relative risk
All antidepressants	1.92
SSRIs or SNRIs	1.88
Tricyclics	2.15
Other antidepressants	0.99

Discussion: Growing evidence links antidepressant use with type 2 diabetes onset in adults, but the association has received little study in younger patients. Mechanisms other than weight gain—e.g., disturbance in glucose homeostasis or increased cellular insulin resistance—may play a role in antidepressant-related diabetes onset. Depression is sometimes associated with weight gain, but in the present study, most patients did not have a diagnosis of depression.

Burcu M, Zito J, Safer D, Magder L, et al: Association of antidepressant medications with incident type 2 diabetes among Medicaid-insured youths. *JAMA Pediatrics* 2017; doi 10.1001/jamapediatrics.2017.2896. From the University of Maryland; and Johns Hopkins Medical Institutions, Baltimore, MD. **Funded by the FDA; and the University of Maryland. The authors declared no competing interests.**

*See Reference Guide.

Dialectical Behavior Therapy for DMDD

In a randomized trial, dialectical behavior therapy (DBT) was feasible and showed preliminary evidence of efficacy in treatment of disruptive mood dysregulation disorder.

Methods: Study subjects were children, aged 7–12 years, clinically referred or recruited from the community. Participants were required to have a diagnosis of DMDD, be stabilized on medication, and be able to receive treatment as outpatients. The sample included children with suicidal ideation or behavior or nonsuicidal self-injury. Children were randomized to receive either DBT or treatment as usual (TAU). DBT consisted of all 4 components of adult DBT—individual therapy, skills training, phone coaching, and therapist team consultation—plus a parent training component. DBT was delivered for a planned 32 weeks of 90-minute weekly sessions, with up to 2 booster sessions per month for the following 3 months. Children in the TAU control group received up to 32 weeks of individual therapy, which was not allowed to incorporate DBT features. The primary efficacy outcome measure was the Clinical Global Impression–Improvement Scale,* with response defined as a final score of 1 or 2. Remission was defined as a Clinical Global Impression–Severity Scale* score of ≤3 in consecutive evaluations at weeks 16, 24, and 32. Feasibility and acceptability were assessed with the Therapy Satisfaction Questionnaire (TSQ)-Parent and Child versions, which assessed the degree to which the program was helpful, child-friendly, and comprehensible.

Results: A total of 43 patients were randomly assigned to treatment (21 to DBT, 22 to TAU). Children in the TAU group typically received multiple interventions, which included supportive therapy, cognitive behavioral therapy, parent training, family therapy, psychodynamic therapy, interpersonal therapy, and motivational enhancement.

Treatment adherence was significantly better with DBT than with TAU; the mean number of sessions attended were 28 and 16 in the groups, respectively. Child and parent satisfaction

measured with the TSQ were significantly higher with DBT than TAU ($p=0.03$ for child ratings; $p=0.001$ for parent ratings). Treatment response was achieved by 19 of 21 DBT patients, compared with 10 of 22 patients receiving TAU (90% vs 46%; $p=0.002$). Nearly twice as many children in the DBT group as in the TAU group achieved remission: 11 and 6 patients, respectively (52% vs 27%; $p=0.09$). At week 32, DBT was also associated with a higher level of functioning, indicated by a 29-point increase versus a 13-point increase in mean Children's Global Assessment scale score, as well as less use of psychotropic medication (19% vs 54%; $p=0.03$). During the 3 months of follow-up, patients in each group attended an average of about 4 booster sessions and benefits were maintained.

Adverse events occurred somewhat frequently, the most common being increased aggression (81 occurrences for DBT and 64 for control treatments). There were 20 and 14 occurrences of suicidal ideation, respectively, and 10 and 2 of nonsuicidal self-injury.

Discussion: The high retention rate in this study is notable given the high treatment demands of DBT and it supports the feasibility and acceptability of this form of therapy in preadolescent children. Early improvement in functioning could help maintain engagement in treatment, and DBT-treated patients in the study experienced a nearly 30% increase in global functioning scores within 8 weeks. While these results are encouraging, additional research to evaluate DBT effects on specific symptom domains is needed in this population.

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

Perepletchikova F, Nathanson D, Axelrod S, Merrill C, et al: Randomized clinical trial of dialectical behavior therapy for preadolescent children with disruptive mood dysregulation disorder: feasibility and outcomes. *Journal of the American Academy of Child and Adolescent Psychiatry* 2017;56 (October):832–840. From Weill Cornell Medicine and New York-Presbyterian Hospital, White Plains, NY; and other institutions. **Funded by the NIMH. Four of 12 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Risk Factors for ADHD plus ODD

Adverse life events and negative influences from parents and peers are risk factors that help predict the development of oppositional defiant disorder in children with ADHD, according to a cross-sectional study.

Methods: Study subjects ($n=246$; mean age, 16 years; 67% boys) were selected from a larger study of >1000 children with ADHD and controls. Children from the larger study who had a diagnosis of comorbid ADHD and ODD were identified and matched for age and gender with children with ADHD only and typically developing controls. The 2 groups with diagnosed disorders were further matched for IQ and ADHD subtype.

Candidate risk factors for ADHD and ODD (see table) were assessed using standardized evaluations and compared between the ADHD group versus controls; the ADHD-plus-ODD group versus controls; and the ADHD-plus-ODD group versus ADHD-only group.

Results: Compared with typically developing participants, parental ADHD was the predominant influence affecting development of ADHD. Adverse life events and maternal smoking were also factors. In dually-diagnosed patients, parental ADHD was again highly influential, as were adverse life events. Birth weight, socioeconomic status, and deviant peer affiliation each made a small contribution.

In comparisons between young people with comorbid ADHD and ODD and those with ADHD alone, 5 significant risk factors each contributed to development of ODD: parental ADHD, adverse life events, socioeconomic status, deviant peer affiliation,

Candidate risk factors for ADHD plus ODD
Pre- and perinatal factors Pregnancy duration Birth weight Maternal smoking
Transgenerational influences Parental ADHD
Postnatal factors Adverse life events Socioeconomic status Deviant peer affiliations Expressed emotion

and parental criticism. Age was not a factor in any of the 3 models, indicating that the effects of the predictors on diagnostic status were independent of the age of participants.

Discussion: These results suggest transgenerational factors contribute strongly to the development of ADHD—i.e., factors such as heritability of ADHD and presumably environmental influences that come with a parent with ADHD. In contrast, postnatal adversities appear to be the primary risk factors for ODD in children with ADHD. Adversity may increase risk of ODD by impairment of brain maturation due to stress, teaching antisocial coping strategies, or causing an overactive sympathetic nervous system. Deviant peers may reinforce the child's antisocial behaviors, and low socioeconomic status may have its effects via poor parenting and deviant socialization processes. Parental criticism may be part of a mutually reinforcing cycle between parent and child in the development of conduct problems.

Noordermeer S, Luman M, Weeda W, Buitelaar J, et al: Risk factors for comorbid oppositional defiant disorder in attention-deficit/hyperactivity disorder. *European Child and Adolescent Psychiatry* 2017; doi 10.1007/s00787.017-0972-4. From Vrije Universiteit Amsterdam, the Netherlands; and other institutions. **Funded by the NIH; and other sources. Three study authors disclosed financial relationships with commercial sources; the remaining 7 authors declared no competing interests.**

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.

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.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) 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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Irritability in Clinical Practice

According to a review from the NIMH, irritability has become a major focus of neuroscience and translational research but remains a challenge in clinical practice. Recognizing irritability as a mood problem, rather than simply a behavioral issue, along with consideration of it in the context of common comorbidities, could improve patient outcomes while reducing unsupported use of antipsychotics.

Irritability is defined, somewhat imprecisely, as an increased proneness to anger relative to peers at the same developmental level. It is recognized in the DSM-5 as a dimensional construct, as a subgroup of oppositional defiant disorder, and as the main characteristic of disruptive mood dysregulation disorder (DMDD). The underlying mechanism is believed to be aberrant responding to frustrative nonreward and threat processing, resulting in anger and, ultimately, downstream problems within the family.

Irritability is a transdiagnostic entity, and regardless of the pathophysiological context, it can be measured in the same way. Instruments for assessing irritability include questionnaires such as the Affective Reactivity Index or the Modified Overt Aggression Scale; semi-structured interviews such as the DMDD Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children; structured interviews such as the DMDD module of the Development and Wellbeing Assessment; and change measures such as the Clinical Global Impression scale for irritability, currently the primary outcome measure in many clinical trials.

For children with irritability, treatment should first address comorbid conditions, using evidence-based therapies such as stimulants for ADHD, as irritability often improves when the underlying disorder is controlled. In parallel with this approach or as a next step, psychological treatments should be considered; parenting interventions for younger children and cognitive behavioral therapy for adolescents have well-supported efficacy. Newer psychological treatment approaches include exposure techniques to increase tolerance for frustration and computer-based interventions such as interpretation bias training. Medications for irritability should be reserved for later stages in many cases.

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Several clinical trials of medications for irritability are underway. The only completed trial, of lithium, found no benefit. SSRIs can curb anger attacks in adults but are less effective in younger patients, and there are concerns about activation, suicidality, and inducing mania. Two atypical antipsychotics, aripiprazole and risperidone, have FDA approval to treat disruptive behaviors in children with autism spectrum disorder, and olanzapine may also be effective. However, because of the adverse effects of these drugs, use should be limited to brief periods only in children who have not experienced response to a series of other treatments.

Stringaris A, Vidal-Ribas P, Brotman M, Leibenluft E: Practitioner review: definition, recognition, and treatment challenges of irritability in young people. *Journal of Child Psychology and Psychiatry* 2017; doi 10.1111/jcpp.12823. From the NIMH, Bethesda, MD; and King's College London, U.K. **Funded by the NIMH; and other sources. The authors declared no competing interests.**

Common Drug Trade Names: aripiprazole—Abilify; olanzapine—Zyprexa; risperidone—Risperdal

Generic ER Methylphenidate: Therapeutic Failure

Approved generic formulations of extended-release (ER) methylphenidate in Canada were associated with a 10-fold higher rate of reported therapeutic failure, compared with branded OROS methylphenidate (*Concerta*). Inequivalence of generic extended-release methylphenidate is also under investigation by the U.S. FDA, which has recommended withdrawal of previously approved generics. The present study examined adverse events reported to Health Canada, primarily, but also analyzed events reported to the FDA.

Methods: Adverse-event reports of therapeutic failure were identified in Health Canada's online reporting system for the 1-year period beginning 8 months following the market approval of branded OROS methylphenidate and generic extended-release methylphenidate. The 8-month lag was intended to reduce the influence of inflated early reports for a new drug. Exposure was quantified as the total number of tablets dispensed, assuming once-daily dosing. Narratives of individual cases were reviewed to characterize the features of therapeutic failure. The authors also conducted a similar analysis of U.S. FDA adverse-events reports involving the authorized generic of OROS methylphenidate (the branded product that is distributed as a generic and that is identical to Canadian branded OROS methylphenidate), comparing it to a generic that was the subject of the FDA investigation.

Results: In both the Canadian and U.S. data, reports of therapeutic failure were about 10 times more frequent with generic than OROS methylphenidate. In the Canadian data, the rates of therapeutic failure per 100,000 patient-years of exposure were 412 with generic ER methylphenidate and 38 with branded OROS methylphenidate (rate ratio,* 10.99). Corresponding numbers from the U.S. data were 69 and 7 per 100,000 patient-years of exposure, respectively (rate ratio, 9.51).

Of the 230 Canadian reports that were individually reviewed, 26% were assessed as probably related and 74% as possibly related to the generic medication, based on recognized causality criteria. No cases were determined to be unrelated. Nearly all patients reported being switched to the generic from branded OROS methylphenidate. The generic was reported as not being effective throughout the day in half of patients, mainly with loss of efficacy in the afternoon. Nearly 14% of reports concerned symptoms of excessive drug exposure, occurring primarily in the morning. Adverse effects on social functioning were reported in 22% of cases. Findings in the U.S. data were similar; however, 29% of reports involved loss of efficacy and 40% involved excessive exposure.

Discussion: In Canada, clinical deterioration after a medication switch is a reportable adverse effect. In both countries, approval of generics is based on the assumption that pharmacokinetic bioequivalence predicts therapeutic equivalence. Adverse-event reports in the U.S.

have led the FDA to revise its bioequivalence standards and to withdraw its designation of 2 extended-release generics as bioequivalent to OROS methylphenidate. The observed adverse effects of generic ER methylphenidate are consistent with pharmacokinetic data indicating an earlier peak and decline of the generic product.

Park-Wyllie L, van Stralen J, Castillon G, Sherman S, et al: Differences in adverse event reporting rates of therapeutic failure between two once-daily extended-release methylphenidate medications in Canada: analysis of spontaneous adverse event reporting databases. *Clinical Therapeutics* 2017;39 (October):2006–2023. From Janssen Inc., Canada; and other institutions. **Funded by Janssen Inc. Canada. All study authors disclosed financial relationships with commercial sources, including Janssen, manufacturer of Concerta and the FDA-authorized generic marketed by Actavis.** See related stories in *Child & Adolescent Psychiatry Alerts* 2014;16 (November):61; and 2015; 7 (November):61–62.

*See Reference Guide.

Pharmacokinetics of Evening-Dosed Methylphenidate

HLD200 is an investigational formulation of methylphenidate designed to provide symptom control beginning in the early morning and lasting throughout the day, following evening administration. Current extended-release methylphenidate formulations leave an important unmet need for coverage in the hours after awakening. The single-dose pharmacokinetics and tolerability of HLD200 were evaluated in a pair of studies, 1 in healthy adults and 1 in children and adolescents.

HLD200 uses a proprietary delivery platform, DELEXIS®, consisting of microbeads with 2 layered coatings surrounding a methylphenidate core. The outer coating is designed to delay release until the drug reaches the ileocolon, based on several aspects of gastrointestinal physiology. The inner coating provides extended release of drug in the colon. Both layers utilize multiple mechanisms to control drug release, minimizing inter- and intra-patient variability.

Participants in the adult study were 12 healthy individuals (6 men) who received 54 mg HLD200 at 9 PM or a morning dose of immediate-release methylphenidate in a randomized crossover fashion. The child/adolescent study included 11 children, aged 6–12 years, and 18 adolescents, aged 13–17 years. After a ≥5-day washout of their ongoing ADHD medication, pediatric patients received a 54-mg capsule of HLD200 at about 9 PM. In both studies, the last follow-up was 48 hours after administration.

Pharmacokinetics were similar in adults, adolescents, and children. Because the dosage was not weight-adjusted, peak concentrations and area under the time-concentration curve were higher in children and adolescents than in adults. In all age groups, average drug exposure was <3% during the 10 hours following administration, from 9 PM to 7 AM. The median time to achieve peak concentrations was about 18 hours post dose in children and 16 hours post dose in adolescents and adults. Inter-patient variability in pharmacokinetics was low, and the drug absorption profile was similar in all age groups. Following administration, after about an 8-hour delay in drug release, plasma methylphenidate concentrations increased rapidly, peaked at 16–18 hours post-dose, and then declined slowly, demonstrating extended-release characteristics. The methylphenidate was eliminated by 48 hours. In children, there were no adverse events judged to be medication related. In adolescents, 5 adverse events were probably or possibly related to medication; most were mild. Sleep-related adverse effects did not occur.

Childress A, Mehrotra S, Gobburu J, McLean A, et al: Single-dose pharmacokinetics of HLD200, a delayed-release and extended-release methylphenidate formulation, in healthy adults and in adolescents and children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2017; doi 10.1089/cap.2017.0044. From the Center for Psychiatry and Behavioral Medicine, Las Vegas, NV; and other institutions. **Funded by Ironshore Pharmaceuticals and Development, Inc. Five of 6 study authors disclosed financial relationships with commercial sources, including 4 with Ironshore; the remaining author declared no competing interests.** See related story in *Child & Adolescent Psychiatry Alerts* 2017;19 (September):49–50.

Hormonal Contraceptives and Suicide Risk

Risk of a suicide attempt was increased 2-fold in young women using hormonal contraceptives in a Danish nationwide cohort. The risk increase was particularly large in adolescents.

Methods: The study cohort consisted of women living in Denmark who turned age 15 years between 1996 and 2013 and who had no prior history of hormonal contraceptive use, suicide attempts, antidepressant use, or psychiatric diagnoses. Contraceptive use was defined as current or recent (within the past 6 months), and former use was defined as discontinuation ≥ 6 months in the past. Study outcomes were a first suicide attempt and completed suicide.

Results: The study population comprised nearly 500,000 women aged 15–33 years. The average follow-up was >8 years, and the mean age during follow-up was 21 years. About half of all women (54%) were current or recent users of hormonal contraceptives.

Compared with never-users, current/recent users of hormonal contraception had a nearly 2-fold elevation in risk for a first suicide attempt and a 3-fold increase in suicide. (See table).

Risk was highest in adolescents and increased rapidly after the initiation of hormonal contraceptives. Risk remained at least doubled until 1 year after initiation, and subsequently subsided to levels that were still 30% higher than in non-users after >7 years of use. Former users of hormonal contraceptives were also found to have increased risk of a first suicide attempt or of completed suicide. Risks were elevated for all types of hormonal contraceptives. Patch, vaginal ring, and progestin-only contraceptives were associated with higher risk than oral combined products.

Discussion: Most previous studies have failed to show an association between hormonal contraceptive use and suicide risk, perhaps because they included women several years after they started using the agents, resulting in selection bias favoring women who can tolerate hormonal contraception. In the present study, the decrease in suicide risk after 1 year of contraceptive use was probably the result of discontinuation by women sensitive to the adverse mood effects of these drugs.

Skovlund C, Mørch L, Kessing L, Lange T, et al: Association of hormonal contraception with suicide attempts and suicides. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.17060616. From the University of Copenhagen, Denmark; and Peking University, China. **Funded by the Lundbeck Foundation; and Rigshospitalet, University of Copenhagen. Three of 5 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

*See Reference Guide.

Adjusted risk of a first suicide attempt and completed suicide [†]	
Outcome	Hazard Ratio*
Suicide attempt	
All current/recent	1.97
15–19 years	2.06
20–24 years	1.61
25–33 years	1.64
Former users	3.40
Suicide	
Current/recent users	3.08
Former users	4.82

[†]Adjusted for age, calendar year, education, polycystic ovary syndrome, and endometriosis

Aripiprazole for Tourette's Disorder

In a manufacturer-sponsored, multinational controlled trial, aripiprazole (*Abilify*) was a safe and effective treatment for tics in children and adolescents with Tourette's disorder.

Methods: Participants received treatment at multiple sites in North America and Europe, were aged 7–17 years, and had a diagnosis of DSM-IV-TR Tourette's disorder. Tics were required to be of at least moderate severity, with baseline Yale Global Tic Severity Scale (YGTSS) scores of ≥ 20 and causing impairment in normal routines. After a washout of previous medications, patients were randomly assigned to double-blind treatment with low- or high-dose aripiprazole

or placebo. In patients weighing <110 lbs, target aripiprazole dosages were 5 mg/day (low) and 10 mg/day (high). Target dosages for those weighing >110 lbs were 10 and 20 mg/day, respectively. The primary efficacy outcome was change from baseline in YGTSS score at week 8. The key secondary efficacy endpoint was the Clinical Global Impression–Tourette’s Syndrome (CGI-TS) Improvement score.

Results: Of 133 patients randomized to treatment, 119 (90%) completed the study. The average baseline YGTSS score overall was about 62. At the 8-week endpoint, YGTSS scores were decreased by 13 and 17 points with low- and high-dose aripiprazole, respectively, compared with a 7-point decrease in the placebo group ($p \leq 0.002$). High-dose aripiprazole was significantly superior to placebo in all study weeks, and low dose in all evaluations except week 2. High-dose was superior to low-dose aripiprazole in weeks 4–8. Superiority of aripiprazole was demonstrated in subgroup analyses based on age (children vs adolescents), initial YGTSS severity, and geographic location; and on YGTSS subscales for vocal tics, motor tics, and impairment. Findings were similar for CGI-TS ratings; 69% and 74% of the low- and high-dose aripiprazole groups were rated as much or very much improved, compared with 38% of the placebo group.

Aripiprazole was associated with higher rates of response than placebo according to the study’s a priori definition of response (i.e., >25% improvement in YGTSS-TTS score or a CGI-TS improvement rating of much improved or better): 74% and 89% of the low- and high-dose groups, respectively, compared with 55% of the placebo group. A more stringent definition of response (i.e., >50% improvement in YGTSS–TTS score) was applied later because of the high response rate in the placebo group. The more stringent response rates were 41% and 57% with low- and high-dose aripiprazole, compared with 17% in the placebo group ($p < 0.02$ and $p < 0.0001$, respectively).

Aripiprazole adverse effects were similar to those observed in other pediatric clinical trials and included sedation, somnolence, and fatigue. No serious adverse events occurred. Study discontinuation for adverse effects occurred most often in smaller children. A total of 14 patients discontinued drug or placebo treatment because of adverse events; 11 of these children weighed <110 lbs and received aripiprazole (2 low-dose, 9 high-dose). Clinically relevant weight gain occurred in 18% of the low-dose aripiprazole group and in 9% of both the high-dose and placebo groups.

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

Sallee F, Kohegyi E, Zhao J, McQuade R, et al: Randomized, double-blind, placebo-controlled trial demonstrates the efficacy and safety of oral aripiprazole for the treatment of Tourette’s disorder in children and adolescents. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (November):771–781. From the University of Cincinnati, OH; and other institutions including Otsuka Pharmaceutical Development & Commercialization, Inc. **Funded by Otsuka. Nine of 10 study authors disclosed financial relationships with commercial sources including Otsuka; the remaining author declared no competing interests.**

*See Reference Guide.

Prenatal Acetaminophen and ADHD Risk

According to the results of a population-based study, long-term maternal use of acetaminophen during pregnancy is associated with a >2-fold increase in risk of ADHD in offspring. The increased risk appears to be independent of maternal indications for acetaminophen use and familial ADHD risk.

Methods: The study, conducted by the Norwegian Institute of Public Health, began with an invitation to all pregnant women in the country to complete a mailed questionnaire at about 18 weeks of gestation. About 40% of invited women agreed to participate. The cohort consisted of

nearly 115,000 children born in 1999 and 2009, about 95,000 mothers, and about 75,000 fathers. Both mothers and fathers completed questionnaires about their acetaminophen use during the 6 months before the pregnancy, indications for use, ADHD symptoms, and other factors. Mothers completed additional questionnaires at the 30th gestational week and again 6, 18, and 36 months after delivery. The study outcome was an ICD-10 diagnosis of hyperkinetic disorder, which requires the presence of both inattentive and hyperactive symptoms, in the offspring between 2008 and 2014.

Results: Nearly half of the women (47%) reported acetaminophen use during pregnancy, and about 2200 children received a diagnosis of hyperkinetic disorder. Preconception acetaminophen use by fathers was associated with a small increase in ADHD risk, but preconception maternal use was not. However, compared with children with no prenatal acetaminophen exposure, those whose mothers reported acetaminophen use during pregnancy had increased risk of developing ADHD (based on unadjusted hazard ratios*) of 17–46%, depending on the number of trimesters exposed. These risks were not diminished after adjusting for pre-pregnancy use by either parent and were reduced slightly after adjustment for parental ADHD symptoms and other potential confounders including indication for use. Risk increased with increasing exposure. Hazard ratios for exposure during 1, 2, or all 3 trimesters ranged from 1.07 to 1.27, and the greatest increase was observed with ≥ 29 days of prenatal use (hazard ratio, 2.20).

Discussion: A possible explanation for the association between ADHD and paternal acetaminophen use is endocrine disruption in the testis, leading to germ line epigenetic effects. ADHD is highly familial; however, the present observations suggest that the association of acetaminophen with ADHD in the offspring occurs regardless of parental ADHD symptoms. In addition, fever and infection, common indications for acetaminophen, may adversely affect neurodevelopment, but these results suggest the indications for maternal use are not a major factor in the association. Finally, the lack of an association with pre-pregnancy maternal use indicates that there is a specific gestational effect, which is consistent with but not proof of causality.

Ystrom E, Gustavson K, Brandlistuen R, Knudsen G, et al: Prenatal exposure to acetaminophen and risk of ADHD. *Pediatrics* 2017; doi 10.1542/peds.2016–3840. From the Norwegian Institute of Public Health, Oslo; and other institutions. **Funded by the European Research Council; the NIH; and other sources. The authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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.

Rate Ratio: A comparison of the rates of a disease/event in 2 groups that differ by demographic characteristics or exposure history. The rate for the group of primary interest is divided by the rate for a 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.

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