

CHILD & ADOLESCENT PSYCHIATRY ALERTS

2016 Issue Collection

How to Search: Use Ctrl-F on your keyboard to search the document [OR](#) Click on the issue date below to jump to that month's issue or an article title to go directly to the article.

January 2016

Cannabis, Brain Maturation, and Schizophrenia, 5
Fatty Acids plus Inositol for Bipolar Disorder, 3
Guanfacine for Functional Impairment, 1
Light Therapy for Depression, 2
Subsyndromal Bipolar Disorder Treatment, 4

February 2016

Antipsychotic Overuse, 10
Asenapine for Mania, 8
Montelukast and Neuropsychiatric Symptoms, 9
Orally Disintegrating Amphetamine Salts, 7
Stimulants and Psychotic Symptoms, 7
Token Economy for Problem Behaviors, 11

March 2016

Antidepressants: Suicidality and Aggression, 14
Beta-Agonists and Autism, 16
Bupirone for Repetitive Behaviors, 16
CBT for Relapse Prevention in Depression, 15
Mindfulness Training in ADHD, 17
Self-Harm Interventions, 13

April 2016

ADHD and Quality of Life, 21
Antipsychotics and Diabetes, 23
Bipolar Prodrome, 19
Group Therapy for Mood Dysregulation, 22
Parent Training for Disruptive Behavior, 20

May 2016

ADHD with Aggression and Negative Mood, 25
Aggression: Pharmacotherapy Review, 26
Brief CBT for Adolescent Depression, 28
Childhood Trauma and Bipolar Disorder, 27
Stimulants for ADHD with Tourette Syndrome, 29
Treating Mood Dysregulation in ADHD, 29

June 2016

Adolescent ADHD Treatments, 31
Antidepressants and Fracture Risk, 35
Atomoxetine and Risk of Suicide, 33
Autism: Potential Biomarker, 32
Suicide Prevention Interventions, 34

July 2016

ADHD: Neural and Genetic Correlates, 37
Antidepressants: Relative Efficacy, 40
Antipsychotics: Cardiac Safety, 39
Methylphenidate: Cardiac Safety, 38
Puberty and Depression Risk, 41

August 2016

Anxiety Treatments, 43
Computer Gaming for Autism, 44
Conduct Disorder Pharmacotherapy, 47
D-cycloserine for OCD, 46
Energy Drinks and Mental Health, 45
Parental Accommodation in Anxiety, 48

September 2016

Agomelatine for ADHD, 51
Brain Development Study Recruitment, 49
Metformin for Antipsychotic Weight Gain, 52
Pharmacotherapy for Opioid Use Disorders, 49
Predicting Underage Drinking, 50
Sertraline-Associated EPS, 53
Stimulants plus Guanfacine for ADHD, 51

October 2016

Brain Stimulation for Depression, 56
Cognitive Psychological Treatment for Tics, 58
Parental Depression: Impact on Offspring, 57
Stimulants and Bone Mass, 55
Suicide in Children and Adolescents, 59

November 2016

Digital Parent Training, 62
Mindfulness-Based Interventions, 61
Paternal Substance Abuse, 65
Psychological Depression Prevention, 63
Stimulants and Adaptive Function, 64

December 2016

ADHD, Bullying, and Psychosis, 67
Disruptive Behavior: Neurobiology, 70
Multifamily Treatment for Anorexia, 69
Negative Symptoms and Cognitive Function, 68
Toddler Aggression: Brief Intervention, 71

CHILD & ADOLESCENT PSYCHIATRY ALERTS

Cannabis, Brain Maturation, and Schizophrenia.....	5
Fatty Acids plus Inositol for Bipolar Disorder.....	3
Guanfacine for Functional Impairment	1
Light Therapy for Depression.....	2
Reference Guide	6
Subsyndromal Bipolar Disorder Treatment	4

Volume XVIII / January 2016 / Number 1

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Guanfacine for Functional Impairment in ADHD

According to a secondary analysis of data from a randomized placebo-controlled trial, once-daily extended-release guanfacine (*Intuniv*) improves functional impairment in children and adolescents with ADHD.

Methods: Study subjects, aged 6–12 years (mean age, 9 years), had a primary diagnosis of ADHD and ADHD Rating Scale–IV and Clinical Global Impression–Severity scores indicating at least moderate severity. Participants were randomly assigned to either placebo or to extended-release guanfacine, administered as a single dose in the morning or evening (because the study was not powered to test the difference between morning and evening dosing, the groups were pooled for analysis). The guanfacine dose was optimized over the first 5 weeks of the study and held stable over the remaining 3 weeks. Functional impairment was measured at baseline and at weeks 5 and 8 using the Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P), a brief rating scale developed specifically for children and adolescents with ADHD that consists of 50 items in 6 domains. A total of 221 patients received guanfacine, and 112 received placebo.

Results: Patients who received guanfacine had significantly larger improvement in WFIRS-P total score than those who received placebo (effect size,* 0.45; $p < 0.001$). Among the 6 domains, guanfacine was associated with improvement in Family, Learning and School (including the subdomains of Academic Performance and Behavior in School), Social Activities, and Risky Activities, with effect sizes ranging from about 0.3 to 0.5 and p values usually < 0.001 . Two domains, Life Skills and Self-Concept, were unaffected by guanfacine treatment. Patients whose ADHD symptoms were responsive to guanfacine or placebo also showed more robust responses in measures of function.

Discussion: Clinical trials of ADHD treatment have largely focused on symptoms of the disorder, but this study and others suggest that treatment benefits may also extend to functional outcomes. In this study, effect sizes for functional domains were in the moderate range

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and slightly lower than those observed for ADHD symptoms. The lack of improvement in Life Skills and Self-Concept suggests that these domains may require more intensive or longer treatment.

Stein M, Sikirica V, Weiss M, Robertson B, et al: Does guanfacine extended release impact functional impairment in children with attention-deficit/hyperactivity disorder? Results from a randomized controlled trial. *CNS Drugs* 2015; doi 10.1007/s40263-015-0291-6. From Seattle Children's Hospital, WA; and other institutions including GlaxoSmithKline, King of Prussia, PA. **Funded by Shire Development, LLC. All 6 study authors disclosed financial relationships with commercial sources.**

*See Reference Guide.

Bright Light Therapy for Adolescent Depression

A 2-week course of adjunctive bright light therapy was feasible and acceptable in adolescent inpatients with moderate-to-severe depression. Both bright light and the control treatment were associated with improvement in depression.

Methods: Study participants were medication-naïve, aged 12–18 years, and admitted to a German pediatric psychiatric hospital with a primary diagnosis of moderate-to-severe depression. All patients received standard multimodal psychological treatments including: individual and group psychotherapy; nursing and medical care; school; occupational therapy; family therapy; and other interventions. Afternoon outdoor activities were also part of standard treatment. In addition to the standard treatment, study participants were randomly assigned to receive either bright light therapy (10,000 lux) or inactive dim light (≤ 150 lux) about 1 week after admission. Both treatments consisted of 45 minutes of morning light exposure 5 times a week for 2 weeks. Multiple outcomes were assessed immediately post treatment and after 3 weeks of follow-up: depression with the Beck Depression Inventory-II (BDI-II), sleep with the German sleep questionnaire SFB/R, and chronotype with the Morning-Evening Questionnaire.

Results: A total of 57 patients received study treatment. Seven patients discontinued the intervention, and 9 others were lost to follow-up by week 3; all were included in the outcome analysis. Baseline depression was moderate in 34 patients and severe in 23; about one-third had a seasonal pattern of depression.

Both treatment groups showed significant improvement in depression according to BDI-II scores ($p < 0.001$), with no difference between the groups. Rates of remission (i.e., BDI-II score < 10) after treatment were 20% with bright light therapy and 11% for controls, a nonsignificant difference. Remission rates at 3 weeks were 47% and 26%, respectively ($p = 0.09$).

Sleep quality and the amount of restorative sleep improved during treatment in the bright light therapy group, but not in the comparison group ($p = 0.007$ and $p < 0.001$, respectively). The control group showed some improvement in sleep quality only between the end of treatment and follow-up. Sleep quality was at least markedly improved in 27% of the bright light therapy group, compared with 7% of controls ($p = 0.03$). Both groups showed continued improvement over follow-up. Short-term remission/improvement in restorative sleep occurred in 50% and 15% of patients, respectively ($p = 0.002$). Shifts toward a "morningness" chronotype occurred earlier and more often in the group receiving bright light therapy. Enhanced sleep quality and chronotype shifts were predictive of greater improvement in depression, while bright light therapy and restorative sleep changes were not.

Discussion: The study interventions were feasible and accepted by both patients and hospital staff. The study may have failed to show superiority of bright light therapy because of a high placebo response rate, the therapeutic effects of other elements of the treatment protocol,

small sample size, and an insufficient observation period. It is likely that improvements in sleep and a shift toward morningness may require more than a few weeks to show antidepressant effects; additional study appears to be warranted.

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

Bogen S, Legenbauer T, Gest S, Holtmann M: Lighting the mood of depressed youth: feasibility and efficacy of a 2 week-placebo controlled bright light treatment for juvenile inpatients. *Journal of Affective Disorders* 2016;190 (January):450-456. From the LWL University Hospital of the Ruhr University Bochum, Hamm, Germany. **Funded by the LWL-Research Institute for Mental Health and Prevention, Bochum, Germany. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

Fatty Acids plus Inositol for Bipolar Spectrum Disorders

In a pilot study, the combination of omega-3 fatty acids and inositol was more effective than either agent alone at reducing symptoms of bipolar disorder in children. The study treatments, which were largely free of adverse effects, may be promising as alternative or augmenting therapy.

Methods: Study participants (n=24) were children, aged 5–12 years, with a diagnosed bipolar spectrum disorder who were experiencing manic symptoms of mild-to-moderate severity but no major delusions or hallucinations. Participants could be experiencing manic, hypomanic, or mixed symptoms when randomized. With the exception of ADHD treatments, concomitant CNS medications were not permitted during the study. Patients were not required to be treatment-naïve, and those with a poor response to their pre-study medications could discontinue them and undergo randomization. Following baseline assessment, children were randomly assigned in double-blind fashion to 12 weeks of 1 of 3 treatments: inositol plus placebo, high-eicosapentaenoic acid (EPA) omega-3 fatty acids plus placebo, or the combination of both active supplements. Double-placebo treatment was not deemed ethical. High-EPA omega-3 fatty acid was given as 6 capsules per day of a commercially available supplement with 325 mg EPA and 225 mg docosahexaenoic acid (DHA) per 2 capsules. Inositol capsules were compounded for the study and dosed at 4 daily 500-mg capsules for children weighing ≥ 55 lbs. and 80 mg/kg for smaller children. Outcome measures included the Young Mania Rating Scale (YMRS), Brief Psychiatric Rating Scale (BPRS), Children's Depression Rating Scale (CDRS), and Clinical Global Impression–Improvement (CGI-I) scale.

Results: A total of 11 patients dropped out of treatment—7 for lack of efficacy and 4 because of poor or non-compliance—but were included in the intent-to-treat analysis. All treatments, and particularly combined treatment, were associated with improvement from baseline in bipolar disorder symptoms. (See table, next page). Combined treatment was generally associated with a higher likelihood of favorable outcomes than the other treatments. Response, defined as a $\geq 30\%$ decrease in YMRS score, occurred more often with combined treatment than either monotherapy (odds ratios* for combined treatment vs. inositol and fatty-acid monotherapies, 1.13 and 3.75, respectively). CGI-I scale ratings of much improved or better also occurred more frequently with combined treatment (odds ratio vs. inositol and fatty-acid monotherapies, 3.11 and 5.83, respectively). Euthymia, defined as a final YMRS score of < 12 , was also more likely with combined treatment (odds ratio vs. inositol and fatty-acid monotherapies, 7.0 and 1.07, respectively).

Patients experienced few adverse events other than gastrointestinal symptoms. The treatments had no effect on weight or cardiovascular parameters, except for a mean 15-point drop in diastolic blood pressure in the inositol monotherapy group.

Change from baseline in measures of mania, general psychopathology, and depression									
Measure	Inositol Monotherapy			Omega-3 Fatty Acid Monotherapy			Combined Inositol-Fatty Acids		
	Baseline	End Point	Effect Size*	Baseline	End Point	Effect Size	Baseline	End Point	Effect Size
YMRS	25	18	1.47	25	19	0.7	25	15	1.27
CDRS	44	37	0.84	40	36	0.4	41	31	1.01
BPRS	46	44	0.21	46	31	1.1	50	30	1.31

Discussion: These study results confirm previous observations with omega-3 fatty acids, while the improvement with inositol is a novel finding. The 2 treatments have complementary mechanisms: Omega-3 fatty acids increase membrane fluidity, and inositol acts as a second messenger in multiple neurotransmitter systems. Effect sizes in this study were generally large, although interpretation is limited by small sample size.

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

Wozniak J, Faraone S, Chan J, Tarko L, et al: A randomized clinical trial of high eicosapentaenoic acid omega-3 fatty acids and inositol as monotherapy and in combination in the treatment of pediatric bipolar spectrum disorders: a pilot study. *Journal of Clinical Psychiatry* 2015;76 (November):1548–1555. From Massachusetts General Hospital, Boston; and other institutions. **Funded by private donors. Three study authors disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

*See Reference Guide.

Treating Subsyndromal Bipolar Disorder

In a pilot study of children with subsyndromal bipolar disorder, individual family psycho-educational psychotherapy (IF-PEP), alone and in combination with omega-3 fatty acids, was acceptable and improved depressive symptoms.

Background: Subsyndromal presentations of bipolar disorder—NOS and cyclothymia—are highly impairing but have no evidence-based treatment guidelines. Nonpharmacologic interventions may have a more favorable risk–benefit profile in subsyndromal patients than currently available drugs.

Methods: Study participants were aged 7–14 years and had a confirmed diagnosis of bipolar disorder NOS or cyclothymia. Those with active suicidal ideation were excluded. Study patients were randomly assigned to 1 of 4 treatment groups: IF-PEP with omega-3 supplementation, IF-PEP with placebo supplementation, omega-3 supplementation plus active monitoring (placebo condition for IF-PEP), or placebo supplementation plus active monitoring. IF-PEP was delivered in 2 weekly sessions (1 parent-only and 1 child–parent), each typically lasting about 45–50 minutes. The treatment was manualized and included workbooks, activity worksheets, and between-session homework. The program included information about the disorder, symptom management, healthy habits, problem-solving skills, and communication skills. Active monitoring consisted of 5 assessments lasting about 90 minutes. Omega-3 fatty acids were provided as 2 capsules twice daily, each containing 350 mg EPA, 50 mg DHA, and 100 mg other omega-3 fatty acids. The study investigated a range of outcomes rated with the Depression and Mania subscales of the Kiddie Schedule for Affective Disorders

and Schizophrenia (KDRS and KMRS, respectively); the Children's Depression Rating Scale-Revised (CDRS-R); and the Young Mania Rating Scale (YMRS).

Results: A total of 23 children participated in the study. All patients had comorbidity, with anxiety, ADHD, and disruptive behavior disorders each affecting $\geq 65\%$. Adherence to study medication was $\geq 89\%$. Families assigned to IF-PEP completed an average of nearly 16 of the 17 planned sessions. All patients completed ≥ 4 weeks of study treatment, and 83% completed the 12-week trial.

Patients randomly assigned to combined therapy had significantly greater improvement in depression measured with the KDRS than the double-control group (effect size, $* 1.70$; $p=0.01$) and the omega-3-only group (effect size, 0.48). Treatment did not differentially affect CDRS-R-rated depression. Manic symptoms declined in all groups, but there were no significant treatment-related differences. Neither monotherapy was significantly superior to combined treatment on any outcome measure, but omega-3 monotherapy had a large effect (0.86) on the YMRS, and IF-PEP monotherapy had a large effect on the KDRS (0.92). Combined therapy was not superior to IF-PEP monotherapy for any outcome.

Discussion: Mainly because of the small sample size, the conclusions that can be drawn from this research are limited. However, compared with available pharmacotherapies, both fatty acid supplementation and IF-PEP have a favorable risk-benefit profile and additional, more rigorous study appears to be warranted.

Fristad M, Young A, Vesco A, Nader E, et al: A randomized controlled trial of individual family psychoeducational psychotherapy and omega-3 fatty acids in youth with subsyndromal bipolar disorder. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (December):764–774. From The Ohio State University, Columbus; and Children's Hospital of Eastern Ontario, Ottawa, Canada. **Funded by the NIMH; and the National Center for Research Resources. Two study authors disclosed financial relationships with commercial sources; the remaining 6 authors declared no competing interests.**

*See Reference Guide.

Cannabis, Brain Maturation, and Schizophrenia

In a population-based study, cannabis use in early adolescence was associated with reduced cortical thickness in boys at high genetic risk for schizophrenia. Cannabis-associated changes in brain structure were not found in boys with low genetic risk scores or in girls.

Methods: Study subjects ($n=1577$) included 3 separate population-based samples of adolescents: 1 Canadian sample assessed at a single time in a cross-sectional manner, and 2 European samples (1 all male, 1 mixed-gender) studied longitudinally through adolescence. All adolescents had marijuana use ascertained, underwent brain MRI imaging between the ages of 14 and 21 years, and had genetic risk for schizophrenia evaluated using a polygenic risk score based on 108 loci identified by the Psychiatric Genomics Consortium. The primary outcome variable was mean cortical thickness, a proxy for the effects of various exposures on cortical neurobiological features, especially certain cell types and capillary densities. The primary exposure of interest was cannabis use before age 16 years. The genetic risk score was explored as a possible mediator of this relationship.

Results: In the Canadian sample, age-adjusted cortical thickness decreased significantly with increasing schizophrenia genetic risk scores in male cannabis users ($p=0.009$), but not in non-users of any gender and just slightly in girls. In the all-male European sample, a significant association was found between reduced cortical thickness and the highest frequency of prior cannabis use (≥ 61 occasions before age 16 years; $p=0.02$) in the adolescents with genetic risk scores above the median. No relationship was demonstrated in young men with low genetic risk. In the other European sample, any cannabis use before

age 16 years, versus no use, and the genetic risk score had an interactive effect on longitudinal changes in cortical thickness. In girls, genetic risk was associated with reduced cortical thickness, but cannabis use did not contribute to this effect. In all 3 population samples, the largest effects of cannabis were found in brain regions with the highest expression of the cannabinoid receptor 1 gene.

Discussion: Two processes might underlie brain thinning in adolescent males at risk of schizophrenia: interference with experience-related brain plasticity and testosterone-driven perturbations of cortical maturation. Cannabis exposure may accelerate these processes.

French L, Gray C, Leonard G, Perron M, et al: Early cannabis use, polygenic risk score for schizophrenia, and brain maturation in adolescence. *JAMA Psychiatry* 2015;72 (October):1002–1011. From the Rotman Research Institute, Toronto, Canada; and other institutions. **Funded by the Canadian Institutes of Health Research; and other sources. One study author disclosed financial relationships with commercial sources; the remaining 37 authors declared no competing interests.**

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.

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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CHILD & ADOLESCENT PSYCHIATRY ALERTS

Antipsychotic Overuse	10
Asenapine for Mania	8
Montelukast and Neuropsychiatric Symptoms	9
Orally Disintegrating Amphetamine Salts	7
Reference Guide	12
Stimulants and Psychotic Symptoms	7
Token Economy for Problem Behaviors	11

Volume XVIII / February 2016 / Number 2

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Orally Disintegrating Mixed Amphetamine Salts

Adzenys XR (extended-release mixed amphetamine salts) has received FDA approval as the first orally disintegrating extended-release product for the treatment of ADHD in children aged ≥ 6 years and adults. The agent was determined to be bioequivalent to *Adderall XR*, and will be available in the same 6 dosage strengths. *Adzenys XR* contains amphetamine in a mixture of immediate-release and polymer-coated delayed-release resin particles; it is not a generic version of *Adderall XR*. Product launch is expected after March 2016.

Neos Therapeutics announces FDA approval of *Adzenys XR ODT*[™] (amphetamine extended-release orally disintegrating tablet) for the treatment of ADHD in patients 6 years and older: first and only approved extended-release orally disintegrating tablet for the treatment of ADHD. [Press release]. Dallas and Fort Worth, TX: Neos Therapeutics, Inc.; Jan. 27, 2016.

Stimulants and Psychotic Symptoms

In children at familial risk of mental illness, stimulant use was associated with high risk of psychotic symptoms, independently of ADHD. These symptoms should not be assumed to be uncommon.

Background: As dopamine agonists, stimulants have the potential to induce psychotic symptoms. Reports of these symptoms have been rare in clinical trials because of stringent patient selection and because they are not systematically assessed. However, ADHD is relatively common in children of parents with severe mental illness. Some concern has been expressed about prescribing stimulants to children of parents with mental illness.

Methods: Psychotic symptoms were investigated in children and their families enrolled in an ongoing study of developmental psychopathology in offspring of parents with major depressive disorder, bipolar disorder, or schizophrenia. The study sample comprised 141 offspring, aged 6–21 years. Psychotic symptoms in the children were assessed in 4 different ways: clinically significant hallucinations or delusions on the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL); positive symptoms on the

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Structured Interview for Prodromal Syndromes (SIPS); self-reported psychotic-like experiences on the "Funny Feelings" Interview; and high-risk profiles on the Schizophrenia Proneness Instrument–Child and Youth Version (SPI-CY). The association between lifetime history of stimulant use and lifetime history of psychotic symptoms was the study outcome.

Results: Of the 141 study participants, 24 (17%) had received treatment with a stimulant medication. Of these, 20 received methylphenidate (*Ritalin*). A clinical diagnosis of ADHD had been assigned to 33 (23%); 17 who received stimulants and 16 who were unmedicated.

A total of 47 participants (33%) had experienced psychotic and related symptoms. The symptoms were present in comparable proportions of children whose parents had schizophrenia, bipolar disorder, and depression. Psychotic-like symptoms occurred in 15 (63%) patients who had taken stimulants and in 32 of 117 (27%) who had not (odds ratio,* 4.43; $p=0.002$). All 15 patients who had taken stimulants and had psychotic symptoms were children of parents with bipolar disorder or major depression. In a multivariate analysis, stimulant use remained associated with psychotic symptoms but ADHD did not, which suggests that the medication rather than the disorder increases the risk of psychotic symptoms. In the patients whose symptoms could be reliably assigned a date, the symptoms showed a strong temporal relationship with stimulant use. In 3 patients who were followed while on and off stimulant medication, the psychotic phenomena coincided with periods of stimulant use.

Discussion: The present study results suggest that children and adolescents who receive stimulant treatment, particularly those with a familial history of schizophrenia, bipolar disorder, or depression, should be monitored for development of psychotic symptoms. Whether these symptoms are predictive of psychotic disorders later in life is unknown.

MacKenzie L, Abidi S, Fisher H, Propper L, et al: Stimulant medication and psychotic symptoms in offspring of parents with mental illness. *Pediatrics* 2016;137 (January):e20152486. From Nova Scotia Health Authority, Halifax, Canada; and other institutions. **Funded by the Canadian Institutes of Health Research; and other institutions. The authors declared no competing interests.**

*See Reference Guide.

Asenapine for Mania

In a manufacturer-sponsored, multicenter, controlled trial, asenapine, an atypical antipsychotic with a novel pharmacologic profile, was superior to placebo in children and adolescents with bipolar I disorder who were experiencing a manic or mixed episode.

Background: Asenapine is a sublingual, second-generation antipsychotic with a novel combination of antagonism for serotonin, dopamine, noradrenaline, and histamine receptors. The agent is FDA approved for monotherapy or as an adjunct to lithium or valproate for manic or mixed episodes of bipolar I disorder in adults and as monotherapy in pediatric patients aged ≥ 10 years.

Methods: Participants in the study, which was conducted as part of a postmarketing requirement, were aged 10–17 years and had a primary diagnosis of bipolar I disorder. All were experiencing a current manic or mixed episode, with or without psychotic features. After other medications were tapered, patients were randomly assigned to 3 weeks of treatment with 2.5, 5, or 10 mg asenapine b.i.d. or placebo. All study medication was administered as a flavored sublingual tablet. The primary efficacy outcome was change from baseline in the Young Mania Rating Scale (YMRS).

Results: A total of 403 patients received randomly assigned medication and were included in the analysis. A somewhat larger proportion of patients were experiencing a mixed rather than manic episode (58% vs. 42%). Small proportions of the 4 groups, 5–13%, had psychotic features, and about half of patients had comorbid ADHD, the most common comorbidity.

Each dose of asenapine was superior to placebo at improving the YMRS total score. Superiority was statistically significant from day 4 onward. Response ($\geq 50\%$ improvement in YMRS total score) occurred in 42–54% of the asenapine groups, compared with 28% of the placebo group. All 3 asenapine doses were also superior with regard to secondary outcomes: the Clinical Global Impression–Bipolar severity score and the Children’s Global Assessment Scale. Effects of asenapine on depression were inconsistent at different doses.

Between 11% and 15% of the 4 groups discontinued treatment before the 3-week study endpoint. Discontinuation rates did not differ among the treatment groups. Most adverse effects observed in this study were similar to those observed with other atypical antipsychotics. The combination of somnolence, sedation, and hypersomnia affected about half of patients who received asenapine, but only 12% of the placebo group. The most common adverse effects of asenapine, whose incidence was at least twice that in the placebo group, were somnolence, sedation, oral hypoesthesia, oral paresthesia, and increased appetite. Asenapine was associated with a higher incidence of significant weight gain (8–12% of the dosage groups) than placebo (1%). Patients who received asenapine had larger increases than the placebo group in fasting insulin, glucose, total and LDL cholesterol, and triglycerides, but these differences generally were not statistically significant. Nine patients, including 1 in the placebo group, reported generally transient suicidal ideation.

Discussion: The authors note that these results may not generalize to the entire population of children and adolescents with bipolar I disorder. In addition, the short duration of the trial does not allow for conclusions on the long-term efficacy or safety of asenapine. However, a 50-week extension of the trial has been completed but findings have not yet been published. Those results will be covered in a future issue.

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

Findling R, Landbloom R, Szegedi A, Koppenhaver J, et al: Asenapine for the acute treatment of pediatric manic or mixed episode of bipolar I disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2015;54 (December): 1032–1041. From Johns Hopkins University and the Kennedy Krieger Institute, Baltimore, MD; and other institutions. Funded by Merck, and Co., Inc. All 9 study authors disclosed financial relationships with commercial sources.

Common Drug Trade Names: asenapine—*Saphris*; valproate—*Depakene, Depakote*

*See Reference Guide.

Neuropsychiatric Effects of Montelukast

According to an analysis of adverse drug events reported to Vigibase, the World Health Organization’s global drug monitoring database, 60% of adverse event reports with the asthma medication montelukast (*Singulair*) are considered psychiatric or central nervous system (CNS) related.

Background: Based on clinical trial data and case reports, the FDA issued an alert regarding psychiatric side effects of montelukast and related drugs in 2008. Elevated incidence of these adverse events has since been reported from several countries. The present study was conducted to explore the association worldwide.

Methods: The analysis included all case reports through January 1, 2015, in which montelukast, alone or as part of a multi-drug exposure, was associated with onset of psychiatric or CNS disorders in patients aged <18 years. The adverse events were examined in infants (aged <2 years), children (aged 2–11 years), and adolescents (aged 12–17 years) for all calendar quarters beginning in 1999 and continuing through January 2015.

Results: The database contained a total of 2630 case reports of a psychiatric disorder in young patients exposed to montelukast, including 114 in infants, 2007 in children, and 509 in

adolescents. There were also 1225 additional reports of "nervous system disorders" in exposed children and adolescents. The most common disorders are listed below. (See table.) Most of the reports included multiple psychiatric adverse events. The average time to onset varied from hours or days for sleep disorders and psychotic disorders, to 1 to several weeks for depression, and from months to years for the suicidal category.

Most common psychiatric disorders associated with montelukast in patients aged <18 years in VigiBase		
Disorder	Number of Cases	Percentage of Cases [†]
Personality disorders and disturbances in behavior	955	36%
Sleep disorders and disturbances	957	36%
Mood disorders and disturbances	955	36%
Anxiety disorders and symptoms	823	31%
Suicidal and self-injurious behaviors	674	26%
Depressed mood disorders and disturbances	608	23%

[†]Total percentage >100% because of reports listing multiple adverse events.

There were statistically significant differences in reports of individual disorders across age categories. Children had the highest incidence of suicidal behavior, sleep disorders, and depressive and psychotic symptoms. The number of events in infants was too low to analyze except for sleep disorders, for which the incidence was significantly elevated. Incidence of depression/anxiety was similar in children and adolescents and twice that found in adults.

Of all VigiBase reports concerning pediatric suicidal and self-injurious behavior, 674 cases (10%) were linked with montelukast. Montelukast was associated with completed suicide in 35 patients. Completed suicide and suicide attempts were most often reported in adolescents, and suicidal ideation in children.

Discussion: Infants and children seem to be more prone to sleep disturbances with montelukast use, whereas adolescents are more prone to symptoms of depression/anxiety and children to psychotic reactions. Suicidal behavior and completed suicide appear to occur more frequently than previously thought. Currently there is no biological explanation for the association of montelukast with psychiatric/CNS adverse effects, and there continues to be a lack of well-designed epidemiologic studies that would shed further light on the link.

Perona A, Garcia-Saiz M, Alvarez E: Psychiatric disorders and montelukast in children: a disproportionality analysis of the VigiBase. *Drug Safety* 2015; doi 10.1007/s40264-015-0360-2. From the Hospital Universitario de Canarias; and the University of La Laguna, Spain. **This study was conducted without funding. The authors declared no competing interests.**

Overuse of Antipsychotics in Children

In children, antipsychotics (particularly second-generation agents) are most often prescribed off-label, typically for nonpsychotic conditions, and where effective and safer alternative medications and psychosocial treatments may exist. The growing use raises concern because of their serious acute adverse effects and unknown long-term effects, according to an opinion article.

Antipsychotics are FDA-approved for use in children to treat schizophrenia, bipolar disorder, and severe behavioral problems associated with autism. However, the most common use of these agents is in children with ADHD. Antipsychotics have been shown to be effective in controlling self-injurious and disruptive behaviors, but mostly in short-term, industry-funded studies. These short-term studies have also raised concerns about adverse effects such as weight gain, metabolic alterations, hormonal effects, neurologic symptoms, and cardiovascular

problems. Monitoring children for these effects is recommended, but compliance with monitoring guidelines is poor. A few studies have suggested these agents have long-term effects on brain development and social functioning. Children are particularly vulnerable because their developing brains and bodies may be permanently altered by these medications. Children, particularly those with developmental disabilities or autism, have difficulties expressing their emotional and physical needs, which antipsychotic treatment can exacerbate.

Alternative treatments to control aggressive behavior include adding a nonstimulant or a stimulant from another class to primary ADHD therapy, manualized parent training, cognitive-behavioral techniques, or, in adolescents, multifocused interventions such as multisystemic therapy. Some of these interventions have effects comparable to those reported with antipsychotics. Behavior problems in children may be related to disruptive parenting and stressful environments, which deserve primary attention.

The overuse of antipsychotics in young patients could be attributed in part to inappropriate pharmaceutical advertising, difficulties in obtaining hospitalization or psychosocial treatments, or a desire to control patients' behavior quickly. The most vulnerable children—those in foster care, juvenile detention, and institutions—are the most likely to receive these medications.

According to the authors, increasing maternal leave, family supports, education of public officials responsible for protecting children, and research on the longitudinal effects of these drugs could potentially reduce the overuse of antipsychotics in young patients. In addition, clinicians should be educated about safer alternatives to antipsychotics and prescribing should be monitored to improve compliance with existing guidelines for treating aggression in young patients.

Daviss W, Barnett E, Neubacher K, Drake R: Use of antipsychotic medications for nonpsychotic children: risks and implications for mental health services. *Psychiatric Services in Advance*: doi 10.1176/appi.ps.201500272. From Geisel School of Medicine, Dartmouth College, Hanover, NH. **The authors declared no competing interests.**

CBT with Token Economy for Problem Behaviors

In a small uncontrolled study, cognitive behavioral therapy with a token-economy system had positive effects on target problem behaviors in children and adolescents with ADHD when used as an add-on to methylphenidate (*Ritalin*).

Methods: Study participants (n=25; mean age, 10 years; 19 boys) were recruited from a university clinic for neurodevelopmental disorders in Brazil. Each had received a new diagnosis of ADHD and had been given a prescription for once-daily long-acting methylphenidate. Simultaneously, patients began a CBT program, consisting of 20 weekly 2-hour group sessions, including about 40 minutes of parent/caregiver training and 80 minutes with the children. The token economy was introduced in the 5th session. Parents and children identified inappropriate behaviors that caused functional impairment in a personal or social context. The 10 most problematic behaviors were rewritten with positive phrases as a guide to what the child should do. Parents monitored the problem behaviors, and at each session the child was rewarded for non-occurrence with a token that could be exchanged for a prize at the end of session 15. Parents also were encouraged to provide non-token rewards, such as praise, activities, trips, and games. Based on an analysis by specialists in CBT and neurodevelopment, the problem behaviors were grouped into 10 categories: impulsiveness; hyperactivity; disorganization; disobeying rules and routine; poor self-care; verbal and physical aggression; easily frustrated; compulsive behaviors; antisocial behavior; and lack of initiative and execution. Inattention was identified as a problem too infrequently to be included in the list of top dysfunctional behaviors. The primary study outcome was change from baseline in each of the problem behaviors, as reported by parents weekly after the 10-week token-economy system was instituted.

Results: After 10 weeks of participation in the token-economy system, statistically significant declines in 7 of the 10 problem-behavior categories were evident. (See table.)

Change in Weekly Frequency of Problem Behaviors			
Behavioral category	Mean weekly frequency at week 1 of token economy	Mean weekly frequency at week 10 of token economy	Statistical significance
Impulsiveness	2.67	0.80	p=0.001
Hyperactivity	1.6	0	p=0.001
Disorganization	1	0.32	p=0.001
Disobeying rules and routines	4.21	0.96	p=0.001
Poor self-care	1.31	0.62	p=0.05
Easily frustrated	3	1.13	p=0.007
Antisocial behavior	1.08	0.08	p=0.001

There were statistically non-significant reductions in verbal and physical aggression, as well as lack of initiative and execution, and no change in compulsive behaviors.

Discussion: In this study, the token-economy system improved both internalizing behaviors (i.e., poor self-care, disorganization) as well as externalizing behaviors (i.e., impulsivity, hyperactivity; disobeying/disrupting routines; poor frustration tolerance; antisocial behavior). With its focus on dysfunctional behaviors reported as problems by parents and children, the intervention might be used to treat a broader range of problems than just the cardinal behavioral symptoms of ADHD. However, because the study sample was small and homogenous, and the results may not generalize to other populations, the results require replication in larger more diverse samples.

Coelho L, Barbosa D, Rizzutti S, Muszkat M, et al: Use of cognitive behavioral therapy and token economy to alleviate dysfunctional behavior in children with attention-deficit hyperactivity disorder. *Frontiers in Psychiatry* 2015; doi 10.3389/fpsy.2015.00167. From the Universidade Federal de Sao Paulo, Brazil. **Source of funding not stated. The authors declared no competing interests.**

Reference Guide

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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Antidepressants: Suicidality and Aggression	14
Beta-Agonists and Autism	16
Buspirone for Repetitive Behaviors.....	16
CBT for Relapse Prevention in Depression	15
Mindfulness Training in ADHD	17
Reference Guide	18
Self-Harm Interventions.....	13

Volume XVIII / March 2016 / Number 3

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Interventions for Self-Harm

There is very little evidence supporting interventions for children and adolescents at risk of self-harm, according to a comprehensive review and meta-analysis.

Methods: A literature search identified randomized controlled trials of psychosocial interventions, pharmacological treatments, or natural products for self-harm. Study subjects were patients, aged ≤ 18 years, who had experienced an episode of intentional self-poisoning or self-injury in the past 6 months resulting in presentation for mental health services. Comparison groups received treatment-as-usual (i.e., enhanced clinical care that did not include the study treatment) or no specific treatment. The primary outcome was repetition of self-harm for up to 2 years post-treatment.

Results: No studies of pharmacotherapy or alternative treatments were identified. The review was based on 11 studies of psychosocial interventions in a total of 1126 patients. Participants had an average age of 15 years, and 80% were girls, reflecting the typical pattern of self-harm in adolescents.

Other than dialectical behavioral therapy for adolescents (DBT-A) and group-based therapy, no treatment was evaluated in >1 study. Many of the trials had a high risk of bias, often due to lack of blinding of participants and study personnel, and reporting of many outcomes was downgraded due to imprecision in effect size estimates. Only 1 trial reported any information on adverse effects of the treatment.

In a total of 7 studies, group-based therapy; individual cognitive behavioral therapy; compliance enhancement; home-based family intervention; and providing an emergency hospital admission card all had no effect on subsequent self-harm. However, many of the studies were small and underpowered. Studies of 3 treatments suggest they may warrant further investigation. DBT-A had no benefit in 1 study, but another found a decrease in self-reported repeated self-harm episodes at 9 and 15 weeks of follow-up. In a single trial, mentalization-based

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therapy was associated with reduced self-harm, but this outcome was based on the use of a structured questionnaire whose interpretation is unclear. In another trial, therapeutic assessment was associated with increased treatment adherence but not with any effect on subsequent self-harm. A single suicide was reported in the psychotherapy groups; there were no suicides in any other treatment group.

Discussion: It is surprising that there have been so few trials of treatments for self-harm, especially given the size of the problem and the known association of self-harm with suicide. The evidence that has been published offers few implications for clinical practice.

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

Hawton K, Witt K, Salisbury T, Arensman E, et al: Interventions for self-harm in children and adolescents. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.:CD012013. doi 10.1002/14651858.CD012013. From Warneford Hospital, Oxford, U.K.; and other institutions. **Funded by Warneford Hospital, Oxford, UK; and other sources. One study author was involved in 1 of the trials reviewed in this report; the remaining 7 authors declared no competing interests.**

*See Reference Guide.

Suicidality and Aggression in Antidepressant Trials

A meta-analysis of clinical study reports confirms the association of suicidality and aggression with antidepressant treatment in children and adolescents.¹

Background: The FDA warnings about suicidality with antidepressant use were based on analyses of published clinical trial manuscripts. Clinical study reports are detailed summaries of trial results, which are submitted for regulatory approval of new drugs. Research has shown that important information on patient outcomes found in clinical study reports was often missing in the published articles.²

Methods: In 2011, the authors requested clinical study reports on SSRIs and SNRIs submitted to the European Medicines Agency and the U.K.'s Medicines and Healthcare Products Regulatory Agency. They did not receive reports for all of the trials or for all of the commonly prescribed drugs and did not receive individual case report forms for any trial. Reports that described double-blind, placebo-controlled trials and contained patient narratives and/or individual patient adverse-effect data (n=68) were included in the analysis. Data was available for only 5 commonly used drugs—duloxetine, fluoxetine, paroxetine, sertraline, and venlafaxine—in a total of 10,258 patients who received an active study drug and 6832 who received placebo; nearly 1400 additional patients received a comparator, either another SSRI or a tricyclic or tetracyclic antidepressant. Of the 68 trials, 11 comprised a child/adolescent sample. The primary outcomes of interest were mortality and suicidality, the latter including suicide, suicide attempt or preparatory behavior, intentional self-harm, and suicidal ideation. Secondary outcomes were akathisia, which has been linked to risk of suicide and violence, and aggression.

Results: The quality of the clinical study reports varied. Individual patient-level adverse event listings were available for 32 trials, and the full protocol for only 44, consistent with regulatory guidance that does not require full submission of all protocols. There were concerns about the validity of the data or fraudulent behavior in 3 trials.

There were 12 patient deaths during the post-randomization phases of the trials, all occurred in adults—8 during SSRI/SNRI treatment and 4 with placebo. Four deaths were misreported by the company, in all cases favoring the investigational drug. A total of 142 suicidality events occurred post-randomization: 86 with an SSRI/SNRI; 7 with imipramine; and 49 with placebo. There were 5 completed suicides (2 each with an active drug or placebo, and 1 with an active comparator). The odds ratio* for any suicidality event in children taking an SSRI/SNRI

versus placebo was 2.39. The risk of aggressive behavior was also elevated during SSRI/SNRI treatment in children, with an odds ratio of 2.79. Akathisia was reported in 30 cases overall, including 5 of 325 SSRI-treated children and adolescents. Incidence was more than twice as high in patients taking active medication than placebo, but the difference was not statistically significant.

Discussion: Limitations—e.g., selection bias; insufficient lead-in periods; insufficient follow-up after treatment; inconsistent coding of serious harms; and exclusion of patients at risk for suicide—make it impossible to unravel the true number of serious harms that occurred during the trials even using the more reliable clinical trial reports.

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

¹Sharma T, Guski L, Freund N, Gotzsche P: Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *BMJ* 2016; doi 10.1136/bmj.i65. From the Nordic Cochrane Centre; and the University of Copenhagen, Denmark. **Funded by the Laura and John Arnold Foundation. The authors declared no competing interests.**

²Wieseler B, et al: Completeness of reporting of patient-relevant clinical trial outcomes: comparison of unpublished clinical study reports with publicly available data. *PLoS Medicine* 2013;10:e1001526.

Common Drug Trade Names: duloxetine—*Cymbalta*; fluoxetine—*Prozac*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor*

*See Reference Guide.

CBT for Depression Relapse Prevention

In adolescents with depression that improved with antidepressant treatment, adding cognitive behavioral therapy to continuation medication resulted in lower likelihood of relapse, even after all treatments were discontinued.¹

Methods: Study subjects were 200 patients, aged 8–17 years, with depression who received treatment with open-label fluoxetine (*Prozac*) for 6 weeks. The 144 patients whose symptoms responded to acute-phase fluoxetine, with a >50% decrease in the Children's Depression Rating Scale–Revised (CDRS-R) score, were randomly assigned to continued medication management either alone (n=69) or with CBT (n=75) for an additional 6 months. CBT was provided weekly for the first month, every 2 weeks for 1 month, and then every 4–6 weeks for the remainder of the continuation period. After week 30, treatment was uncontrolled and patients were followed for up to 48 additional weeks. Study outcomes were time to remission and rate of relapse, determined through clinical interview and the A-LIFE, an adaptation of the Longitudinal Interval Follow-up Evaluation.

Results: Patients were an average age of 14 years at the start of therapy, and nearly 80% were adolescent (aged ≥12 years). As previously reported, remission rates at week 30 were >80%.² A total of 67% remained in follow-up through week 52, and 57% through week 78. Duration of antidepressant therapy averaged about 50 weeks, with 93% of those who remained in follow-up continuing antidepressants beyond 30 weeks.

A total of 121 patients achieved remission at some time during the 78-week study, with no significant differences between groups. However, among the patients who achieved remission, those who received CBT had a significantly lower risk of relapse than those who received medication alone (adjusted hazard ratio,* 0.467; p=0.009). The mean time to relapse was 64 weeks with combined therapy and 51 weeks with medication management alone (p=0.007). Cumulative rates of relapse at week 78 were 36% for combined therapy and 62% for medication alone (p=0.015).

Discussion: Current guidelines for pediatric depression recommend starting therapy with medication, psychotherapy, or both. Results of this study suggest that adding CBT after

patients have experienced response to medication, contrary to the usual practice of reducing the frequency of therapy sessions at that time, may produce better longer-term outcomes. In addition, providing CBT to patients who are already in remission might increase the cost-effectiveness of the therapy by reducing the number of sessions needed.

¹Emslie G, Kennard B, Mayes T, Nakonezny P, et al: Continued effectiveness of relapse prevention cognitive-behavioral therapy following fluoxetine treatment in youth with major depressive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2015;54 (December):991–998. From the University of Texas Southwestern Medical Center; and Children's Medical Center, Dallas. **Funded by the NIMH. One study author disclosed financial relationships with commercial sources; the remaining 7 authors declared no competing interests.**

²Kennard B, et al: Cognitive-behavioral therapy to prevent relapse in pediatric responders to pharmacotherapy for major depressive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2008;47:1395–1404.

*See Reference Guide.

Beta-Agonist Exposure and Autism Risk

Fetal exposure to anti-asthmatic β -2-adrenergic agonist drugs was associated with increased risk of autism, according to a population-based study from Denmark. However, the overall risk of autism is estimated to be small, and uncontrolled maternal asthma may also be harmful to the fetus.

Methods: The study cohort consisted of >600,000 children born in 1997–2006. They were singletons delivered between 23 and 43 weeks gestation. All children from the birth cohort with an autism spectrum disorder diagnosis before mid-2011 were identified and matched with up to 10 controls, based on month and year of birth. Exposure to β -2-agonists was determined from a drug prescription register that did not include hospital pharmacies and therefore did not include the off-label use of these agents as tocolytics in the third trimester. Exposure windows were the 90 days before conception and each trimester of pregnancy.

Results: A total of 5200 children with autism were identified. β -2-agonists were used in 3.7% of cases and in 2.9% of controls. Exposure to these drugs was associated with increased risk of autism (odds ratio,* 1.3). Risk estimates did not vary with exposure over the 3 trimesters of pregnancy, and adjusting for maternal asthma did not change the effect estimates.

Discussion: The association of β -2-agonists with childhood autism is plausible. These drugs can cross the placenta and affect the fetal brain by disrupting replication or differentiation of neurons. Their effects are not trimester-specific, and there may be multiple windows of vulnerability throughout pregnancy. However, an association on the order of that seen in the present study would explain <1% of autism cases in the population.

Gidaya N, Lee B, Burstyn I, Michael Y, et al: In utero exposure to β -2-adrenergic receptor agonist drugs and risk for autism spectrum disorders. *Pediatrics* 2016; doi 10.1542/peds.2015-1316. From Drexel University, Philadelphia, PA; and the University of Copenhagen, Denmark. **Funded by Drexel University. The authors declared no competing interests.**

*See Reference Guide.

Low-Dose Bupirone for Repetitive Behavior

In a randomized trial, low-dose bupirone (*BuSpar*) reduced restricted and repetitive behaviors in children with autism spectrum disorder (ASD). Its overall effects on core symptoms of autism were not significant, however.

Background: There is strong evidence that elevated serotonin levels in the blood may be implicated in the development of ASDs in at least a subset of patients. Bupirone was investigated in the present study because its profile as a partial agonist of serotonin 5HT_{1A} suggests it might be useful in targeting core symptoms of autism in young children during a developmental period when serotonin synthesis capacity is typically low in those with this disorder.

Methods: The study enrolled 166 children, aged 2–5 years, with DSM-IV-TR ASDs. Patients with other conditions that required centrally active medications were excluded. Study patients were randomly assigned to treatment with 2.5 or 5 mg buspirone b.i.d. or placebo. After 24 weeks, patients randomized to buspirone continued at the same dosage and those in the placebo group were re-randomized to 1 of the 2 buspirone groups for an additional 24 weeks. The primary study outcome was the Autism Diagnostic Observation Schedule (ADOS) composite total score. The ADOS subscale for restrictive and repetitive behavior was a secondary outcome measure.

Results: A total of 142 patients completed the first study phase, and 138 began phase 2; a total of 24 patients discontinued treatment during the 48-week study. All groups showed significant improvement over time in core symptoms of autism measured with the ADOS composite total score; outcomes did not differ significantly among the treatment and placebo groups. In contrast, the ADOS restrictive and repetitive behavior scores showed a significant improvement in children who received 2.5 mg buspirone ($p=0.003$), but not in those who received the higher dose or placebo. Other secondary outcome measures did not show a consistent pattern of response.

Tryptophan metabolism in the CNS was assessed at baseline with PET scans in a subgroup of 119 patients. A lower number of focal regions of increased brain tryptophan metabolism was correlated with improvement in restrictive and repetitive behavior, but only in the children who received 2.5 mg buspirone. A total of 60 children, nearly half of the sample, had elevated blood serotonin concentrations. Those in the 2.5-mg buspirone group with normal blood serotonin levels were significantly more likely to improve on the ADOS restrictive and repetitive behavior measure than those with elevated serotonin.

Discussion: Based on these results, further investigation of low-dose buspirone as an adjunct to early behavioral intervention that targets other core symptoms in the areas of socialization, language skills, and adaptive behavior appears to be warranted in young children with autism.

Chugani D, Chugani H, Wiznitzer M, Parikh S, et al: Effect of low-dose buspirone for restricted and repetitive behavior in young children with autism spectrum disorder: a randomized trial. *The Journal of Pediatrics* 2015; doi 10.1016/j.jpeds.2015.11.033. From Wayne State University School of Medicine, Detroit, MI; and other institutions. **Funded by the National Institute of Neurological Disorders and Stroke. The authors declared no competing interests.**

Mindfulness Training in ADHD

Training in mindfulness meditation is a promising therapy with the potential to improve residual symptoms in adolescents and adults with ADHD, according to a literature review.

Although pharmacotherapy for ADHD is highly effective, most patients have impairing residual symptoms. As patients reach adolescence, hyperactivity symptoms abate somewhat while symptoms of inattention persist and may become more disabling. Inattention is marked by distractibility, carelessness, forgetfulness, and organizational difficulty. Adolescents with ADHD have difficulty focusing on tasks, reading, or lectures, and school and job performance and relationships suffer.

Mindfulness, derived from Eastern meditation practices, is a technique of focusing attention on the present moment. It is now a recognized and even manualized psychotherapy, first used for treatment of chronic pain and now used in other clinical populations, including some limited application in adults and adolescents with ADHD. Mindfulness training teaches 2 basic techniques: focused meditation, which leads to less distractibility, and open monitoring or receptive attention, which extends attention to the whole field of awareness and enhances attention switching, self-regulation, and impulse control.

Studies in healthy populations suggest that mindfulness training can improve performance on task completion, self-regulation, and impulse control, areas that represent core symptoms of ADHD. According to one theory, the attention system is supported by 3 components: alerting, which sustains a state of vigilance; orienting, which selects relevant environmental information and enables a quick reaction to a situation; and conflict monitoring, which prioritizes conflicting stimuli. Mindfulness training may improve attention by acting on all 3 of these processes.

The clinical use of mindfulness training in patients with ADHD is in its infancy. A feasibility study of an 8-week program, the Mindful Awareness Program, conducted in 8 adolescents and 24 adults, showed favorable results, but the study lacked a control group. Another feasibility study was conducted in 11 adults, this time with an untreated control group of the same size. Two-thirds of participants in active treatment reported a $\geq 30\%$ reduction in inattention and hyperactivity symptoms, compared with no participants in the control group. This research indicates that mindfulness training is feasible and acceptable in ADHD, but controlled trials are necessary to strengthen the evidence of its usefulness.

Modesto-Lowe V, Farahmand P, Chaplin M, Sarro L: Does mindfulness meditation improve attention in attention deficit hyperactivity disorder? *World Journal of Psychiatry* 2015;5 (December 22):397–403. From Connecticut Valley Hospital, Middletown, CT; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

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.

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.

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CHILD & ADOLESCENT PSYCHIATRY ALERTS

ADHD and Quality of Life.....	21
Antipsychotics and Diabetes	23
Bipolar Prodrome	19
Group Therapy for Mood Dysregulation.....	22
Parent Training for Disruptive Behavior.....	20
Reference Guide	24

Volume XVIII / April 2016 / Number 4

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Identifying a Bipolar Prodrome in Young People

A small subset of dimensional symptoms was useful in predicting the onset of bipolar disorder in a longitudinal study of children and adolescents with a parent who had bipolar disorder.

Methods: The ongoing Pittsburgh Bipolar Offspring Study enrolled parents with bipolar I or II disorder and their children, aged 6–18 years, as well as control families matched for parent age, gender, and neighborhood. Children were assessed at baseline and during follow-up visits every 2 years using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL), the Child Behavior Checklist, and other symptom rating scales. Using factor analyses,* the investigators extracted the symptoms reported in each questionnaire and combined them into 9 different dimensions within 3 categories: parent report (internalizing, externalizing, and inattention/disinhibition), child report (internalizing, externalizing, and affective lability), and a depression rating scale (depressive/atypical symptoms, sleep problems, and suicidality). Statistical analyses of potential predictors of bipolar-disorder onset were based on both baseline values and values from the proximal (most recent) visit before the child met diagnostic criteria for bipolar disorder.

Results: The sample consisted of 33 children with bipolar disorder at baseline, 326 who were at risk, and 220 controls. The study children had a mean age of 12 years at enrollment and nearly 20 years at last follow-up. During the study, 44 at-risk youth had onset of a bipolar spectrum disorder, at a mean age of 15 years. The majority, 29 patients, had bipolar disorder NOS, most with either subthreshold manic symptoms for ≥ 30 days or full criteria for a minimum of 2 days during a single week.

Conversion to bipolar disorder was associated with several factors present at the baseline visit. A multivariate analysis showed that the strongest baseline predictors were parent-reported internalizing symptoms ($p=0.009$) and child-reported affective lability ($p=0.05$). Predictors of bipolar-disorder onset in the proximal visit were child-reported affective ability ($p=0.05$) and the K-SADS Mania Rating Scale score ($p<0.001$). Of the 3 affective lability subscales, irritability

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was the most important predictor of bipolar disorder from both the baseline and the proximal visit. An analysis of symptom trajectories showed that group differences in internalizing and affective lability were consistent across time, but K-SADS Mania Rating Scale scores increased over time for those in whom bipolar disorder developed.

These factors were strongly predictive of outcome when grouped together. At-risk youths with low baseline levels of affective lability, anxiety/depression, and manic symptoms (≥ 1 standard deviation below the mean) and with older parent age of bipolar onset had only a 2% chance of conversion to bipolar disorder over follow-up. Those with high levels of these symptoms and a parent with a younger age of bipolar-disorder onset had a 49% chance of conversion—a 24-fold higher risk.

Clinical Implications: At the initial clinic visit, anxiety/depression and affective lability should raise suspicion that bipolar disorder might develop in an at-risk child, particularly if the affected parent had early onset of the disorder. As these patients are followed, the persistence of affective lability and the emergence of subthreshold manic symptoms markedly increase the risk of conversion to a bipolar spectrum disorder within the next few years. These patients may benefit particularly from increased surveillance and early intervention.

Hafeman D, Merranko J, Axelson D, Goldstein B, et al: Toward the definition of a bipolar prodrome: dimensional predictors of bipolar spectrum disorders in at-risk youths. *American Journal of Psychiatry* 2016; doi 10.1176/appi.ajp.2015.15040414. From the University of Pittsburgh, PA; and other institutions. **Source of funding not stated. Six study authors disclosed financial relationships with commercial sources; the remaining 7 authors declared no competing interests.**

*See Reference Guide.

Internet-Assisted Parent Training for Disruptive Behavior

In a randomized trial, an Internet-assisted parent training program improved behavioral outcomes in 4 year olds with disruptive behavior.

Background: Parent training is a well-validated but infrequently used treatment for childhood behavioral problems. An Internet-based program could reduce barriers to standard office-based parent training such as stigma, low availability, high cost, and logistical problems.

Methods: The study was conducted in Finland, where nearly all children receive an annual comprehensive health assessment before the start of school. All 4-year-old children in the participating municipalities were screened, and those whose parents identified behavior problems for the last 6 months were referred for the study. Enrollment criteria included a score in the highest 80th percentile of the conduct problems subscale of the Strengths and Difficulties Questionnaire and a positive parent response to a single question about the child's behavioral difficulties. Children with developmental disabilities were not enrolled. The study provided computers to families that did not have one. Participating families were randomly assigned to use either the Strongest Families Smart Website (SFSW) or to an educational control.

The evidence-based Strongest Families telephone program was altered to fit an Internet format for the study and accompanied by weekly 45-minute telephone coaching sessions. Parents were encouraged to complete 11 weekly online sessions personalized with the child's name, problems, strengths, and preferred activities. The web content included exercises, instructional videos, and audio clips demonstrating the application of new skills. Children did not participate in coaching or use the website. Parents received booster phone sessions 7 and 10 months after randomization. Parents in the control group were given access to an informative website about positive parenting and a single 45-minute telephone coaching session. The primary study outcome was the 24-item externalizing subscale of the Child Behavior Checklist (CBCL) version for preschool children, administered at baseline and 6 and 12 months after randomization.

Results: The final sample consisted of 464 families. None of the children received psychotropic medication at any point in the study, but 12% of the parent training group and 19% of the comparison group received additional treatment between the start of the study and 12-month follow-up.

Compared with the control treatment, Internet-assisted parent training was associated with significantly larger reductions in CBCL total, externalizing, and internalizing scores from baseline to 6 months. (See table.) These improvements were maintained at 12 months.

CBCL Outcomes at 6 and 12 Months									
	Control Group			SFSW Group			Between-group significance at 6 months	Between-group significance at 12 months	Effect size* at 12 months
	Baseline	6 Months	12 Months	Baseline	6 Months	12 Months			
Total	44.1	35.8	35.8	44.6	30.6	28.8	p<0.001	p<0.001	0.37
Externalizing	19.3	16	15.3	19.8	14	13	p<0.001	p<0.001	0.34
Internalizing	10.5	8.6	9.4	10.6	7.3	7.1	P=0.02	p<0.001	0.35

Children who received the study program also showed greater improvement in 5 of the 7 CBCL symptom domains (i.e., aggression, sleep, withdrawn, anxious, and emotional) at the 12-month assessment. Scores measuring callousness on the Callous-Unemotional Scale also showed larger improvement with the study intervention. Parenting Scale measures had significantly larger improvement with Internet-assisted parent training. At 12-month follow-up, only 19% of children from the parent-training families and 34% of controls continued to be above the 80th percentile threshold for CBCL externalizing behavior.

Discussion: Given their flexibility, anonymity, and ease of access, remote interventions may have important benefits for reaching at-risk individuals who would otherwise not receive treatment. Results of this study support the feasibility and efficacy of Internet-assisted parent training for children with disruptive behaviors.

Sourander A, McGrath P, Ristkari T, Cunningham C, et al: Internet-assisted parent training intervention for disruptive behavior in 4-year-old children: a randomized clinical trial. *JAMA Psychiatry* 2015; doi 10.1001/jamapsychiatry.2015.3411. From the University of Turku, Finland; and other institutions. **Funded by the Academy of Finland; the Canadian Institutes of Health Research; and other sources. Three study authors disclosed financial relationships with commercial sources; the remaining 9 authors declared no competing interests.**

*See Reference Guide.

Quality of Life in ADHD

ADHD has a significant negative effect on health-related quality of life (HRQoL), as reported by affected children and their parents. Notably, the negative effects of ADHD observed in this study were larger than those measured in children with type 1 diabetes.

Methods: The aim of this cross-sectional study was to measure the effects of ADHD on HRQoL in a representative patient population, using 2 validated non-disease specific measurement instruments. The study was conducted in patients aged 6–16 years receiving treatment at an ADHD clinic (n=213), a diabetes clinic (illness control group; n=58), and a dental clinic (healthy control group; n=117). Children with most comorbid mental conditions were excluded from the ADHD group, but those with disorders like oppositional defiant disorder or conduct disorder were included to increase the representativeness of the sample. HRQoL was measured with the child and adult versions of the Pediatric Quality of Life Inventory (PedsQL), with 4 domains (physical, emotional, social functioning, and school functioning) and a total score; and child and adult versions of the Child Health and Illness Profile–Child Edition (CHIP-CE), with

5 domains (satisfaction, comfort, resilience, risk avoidance, and achievement). Disease severity was measured using the ADHD Rating Scale-IV (ADHD-RS-IV).

Results: For the total score and every individual domain of both the child- and parent-rated PedsQL, children with ADHD had significantly poorer scores than children with diabetes and healthy controls ($p < 0.001$ for all comparisons). In most cases, children with diabetes did not have poorer HRQoL than healthy children. Effect sizes* for the comparisons with control children were large, ranging from 0.96 to 2.08 for parent ratings and from 0.57 to 1.37 for child ratings; effect sizes for comparisons with children with diabetes were only slightly smaller. Children with ADHD also had significantly poorer HRQoL ratings on all domains of the parent-rated CHIP-CE and most domains of the child-rated version (except satisfaction and resilience). Severity of ADHD symptoms was significantly correlated with all parent ratings and most child ratings on the HRQoL scales, although correlations were in the low-to-moderate range.

Coghill D, Hodgkins P: Health-related quality of life of children with attention-deficit/hyperactivity disorder versus children with diabetes and healthy controls. *European Child and Adolescent Psychiatry* 2016;25 (March):261–271. From the University of Dundee, Scotland; Shire, Wayne, PA; and Ninewells Hospital and Medical School, Dundee. **Funded by Shire Development, LLC. Both study authors declared financial relationships with commercial sources.**

*See Reference Guide.

Integrative Group Therapy for Severe Mood Dysregulation

In a randomized trial, a group therapy program that integrates components of several approaches reduced irritability in children with severe mood dysregulation (SMD) and ADHD.

Background: The NIMH criteria for SMD were modified slightly to create the diagnosis of disruptive mood dysregulation disorder in DSM-5, eliminating the hyperarousal criterion. The lack of evidence-based treatment for this condition has been linked to increased prescribing of atypical antipsychotics in children with ADHD.

Methods: Study subjects ($n=56$) were children, aged 7–12 years, with SMD and the combined type of ADHD. Criteria for SMD included marked irritability episodes ≥ 3 times a week, abnormal mood (anger or sadness) present at least half of most days, and multiple manifestations of hyperarousal, with symptoms that persisted for ≥ 1 year and were severely impairing. To identify a patient population distinct from children with oppositional defiant disorder, participants were also required to have scores at least as high as the remission criteria on the Children's Depression Rating Scale–Revised (CDRS-R) or the Young Mania Rating Scale (YMRS), 27 and 12 points, respectively.

Before randomization, physicians optimized each child's ADHD medications. Those who continued to meet study criteria were randomly assigned to the experimental therapy, called AIM, or to a community psychosocial care control group. The AIM treatment integrated components from cognitive behavioral therapy for mood disorders, parent training for oppositional behaviors, and social-cognitive programs for aggression. Therapy was conducted in 11 sessions, with parents and children meeting simultaneously in separate groups working on complementary material. The community care group was encouraged to seek community-based therapy. The primary efficacy outcome was change in clinician-rated mood symptoms, measured with the Mood Severity Index (MSI). Secondary outcomes included the CDRS-R, the YMRS, and the parent-rated Disruptive Behavior Disorder Rating Scale (DBDRS). All participants were evaluated at the end of treatment, and the AIM group was assessed again 6 weeks later.

Results: Families who received the AIM intervention attended a mean of nearly 10 group sessions, and only 2 attended $\leq 50\%$ of the sessions. Of the parents, 97% said they would

recommend the treatment, 90% rated the demands of therapy as acceptable, and 80% and 90% reported that it helped them manage their child's behavior or emotional reactivity, respectively.

Compared with community-based care, AIM was associated with a significant improvement in the MSI score when the analysis was limited to the 29 participants who attended the majority of sessions (effect size, * 0.53). Scores continued to decrease in the AIM group during the 6-week follow-up. Irritability scores on the parent-rated DBDRS decreased to a greater extent in the AIM group ($p=0.0234$; effect size, 0.63). The greatest improvement was observed on the "often angry" item (effect size, 0.73), followed by the "often loses temper" (effect size, 0.47) and "easily annoyed by others" (effect size, 0.27) items. Effects on other parent- or teacher-rated behavioral outcomes were small or mixed.

Most participants in the AIM group (95%) had CRDS scores of ≥ 28 at baseline. Scores decreased over time (effect size, 0.51) but reached significance only in participants attending the majority of therapy sessions ($p=0.04$). The largest improvements were seen in the in the social withdrawal, tearfulness, self-esteem, irritability, sleep, and depressed feelings items of the CDRS. Nearly 60% of patients had elevated YMRS scores at baseline. Scores decreased over time, but with no significant difference between the AIM and community care groups.

Discussion: The present study indicates that tailored psychosocial treatments may be a valuable adjunct to stimulant medication in children with ADHD and SMD, one that could be implemented before prescribing an antipsychotic.

Waxmonsky J, Waschbusch D, Belin P, Li T, et al: A randomized clinical trial of an integrative group therapy for children with severe mood dysregulation. *Journal of the American Academy of Child and Adolescent Psychiatry* 2016;55 (March):196–207. From Pennsylvania State University College of Medicine, Hershey, PA; and other institutions.

Funded by the NIMH. Five study authors declared financial relationships with commercial sources; the remaining 10 authors declared no competing interests.

*See Reference Guide.

Antipsychotic Exposure and Type 2 Diabetes

Exposure to antipsychotic drugs was associated with a more than 2-fold increase in the incidence of type 2 diabetes in young people with psychiatric disorders, according to a meta-analysis.

Methods: The meta-analysis included longitudinal studies that reported the incidence of type 2 diabetes in patients aged ≤ 24 years who were exposed to antipsychotic drugs for ≥ 3 months. When available, diabetes-incidence data were included from psychiatric controls or from healthy controls.

Results: The meta-analysis included 13 studies with a total of $>185,000$ young antipsychotic-exposed patients. Most studies ($n=11$) were retrospective, all were of generally high quality, and there was no evidence of publication bias. The mean patient age was 14 years, and the mean length of follow-up was 1.7 years. About half of the antipsychotic-exposed patients had a disruptive behavior disorder or ADHD; mood spectrum disorders were also common, and about 6% had a psychotic disorder. A total of 95% of the exposed patients used second-generation antipsychotics.

Diabetes risk was highest in patients who received antipsychotics and intermediate in psychiatric controls. (See table, next page.) Compared with psychiatric controls, these rates translate to an excess of about 3 cases of type 2 diabetes per 1000 treated patients and a number needed to harm* of 322. In a multivariable analysis, diabetes risk was significantly greater in male patients, those who received olanzapine (*Zyprexa*), and in those with longer follow-up durations.

Unadjusted cumulative risk of type 2 diabetes in youth			
	Antipsychotic-exposed	Psychiatric controls	Healthy controls
Cumulative diabetes risk/1000 patients	5.72	2.61	2.15
Odds ratio* vs. healthy controls	2.58	1.57	—
Diabetes incidence/1000 patient-years	3.09	1.74	1.28
Incidence rate ratio* vs. healthy controls	3.02	2.03	—

Discussion: The elevated rate of type 2 diabetes in psychiatric controls relative to healthy controls probably reflects unhealthy behaviors and the effects of other psychoactive medications. Although diabetes onset remains an uncommon occurrence, it is the most severe outcome of an interaction of drug, genetic, and lifestyle effects in mentally ill youth that include insulin resistance and obesity. These outcomes lead to serious health risks, especially when they start early in life. Clinicians should balance these risks against the potential benefits of antipsychotics, exhaust lower-risk treatment alternatives first, and routinely monitor patients for weight gain and metabolic abnormalities. Olanzapine treatment and exposure time to antipsychotics are major modifiable risk factors.

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

Galling B, Roldan A, Nielsen R, Nielsen J, et al: Type 2 diabetes mellitus in youth exposed to antipsychotics: a systematic review and meta-analysis. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2015.2923. From Zucker Hillside Hospital, North Shore-Long Island Jewish Health System, Glen Oaks, NY; and other institutions. **Funded by the hospital; the NIMH; and other sources. Twelve study authors declared financial relationships with commercial sources; the remaining 6 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.

Factor Analysis: A statistical process in which the values of observed data are expressed as functions of a number of possible causes in order to find which are the most important.

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

Odds Ratio: A comparison of the probability of an event in 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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CHILD & ADOLESCENT PSYCHIATRY ALERTS

ADHD with Aggression and Negative Mood.....	25
Aggression: Pharmacotherapy Review	26
Brief CBT for Adolescent Depression	28
Childhood Trauma and Bipolar Disorder.....	27
Reference Guide	30
Stimulants for ADHD with Tourette Syndrome	29
Treating Mood Dysregulation in ADHD.....	29

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Stimulants in ADHD with Aggression and Negative Mood

According to an analysis of data from 2 clinical studies, stimulant monotherapy resulted in improvement in aggressive behavior in children with ADHD, a disruptive behavior disorder, and chronically irritable or angry mood. These results argue against the early use of second-generation antipsychotics in these children before stimulant treatment has been optimized.

Background: It has become common in recent years for children with disruptive behavior and chronically irritable or angry mood to receive a diagnosis of bipolar disorder. Disruptive mood dysregulation disorder (DMDD), proposed in part as an alternative diagnosis, requires a chronically irritable mood that persists between temper outbursts. This analysis was conducted to compare treatment results in children with and without a persistent negative mood.

Methods: Data were collected from 2 clinical trials of adjunctive medication in children with ADHD and a disruptive behavior disorder that was not responsive to primary stimulant treatment. Following a washout of any previous medications, participants (n=156), aged 6–13 years, were entered into the optimization phase of the study. All were started on OROS methylphenidate, with an optional daily dose of shorter-acting methylphenidate. Children whose symptoms did not respond were switched to extended-release amphetamine-dextroamphetamine. In addition, all families received the Community Parent Education program. The trial's primary outcome, aggression, was measured using the Retrospective-Modified Overt Aggression Scale (R-MOAS), a parent report of the frequency of different types of aggressive behavior. Persistent negative mood was measured using 14 items compiled from other instruments. A factor analysis of the 14 items identified 2 factors: sadness/anhedonia and irritability/low frustration tolerance.

Results: Mean time to stimulant optimization was 70 days, and at this point 51% of children met criteria for remission of aggressive behavior, and 13.5% had aggression that was below the studies' criteria for randomization to adjunctive medication. Nearly one-third of the participants had symptoms that met diagnostic criteria for DMDD at baseline. About three-fourths of

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these subjects were frequently angry or easily frustrated. Among the 14 negative mood items, 2 were associated with higher baseline aggression: flat affect and proneness to angry outbursts. None of the individual baseline symptoms was predictive of remission of aggression.

Discussion: Results of this study indicate that presence of symptoms consistent with DMDD do not contraindicate stimulant therapy as initial treatment. However, aggression may not improve sufficiently in nearly one-third of children, who may then require augmentation pharmacotherapy and extended behavioral interventions.

Blader J, Pliszka S, Kafantaris V, Sauder C, et al: Prevalence and treatment outcomes of persistent negative mood among children with attention-deficit/hyperactivity disorder and aggressive behavior. *Journal of Child and Adolescent Psychopharmacology* 2016;26 (March):164–173. From the University of Texas Health Science Center at San Antonio; and other institutions. **Funded by the NIMH; and other sources including Abbott Laboratories. Five study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

Common Drug Trade Names: methylphenidate—*Ritalin*; amphetamine-dextroamphetamine—*Adderall*; OROS methylphenidate—*Concerta*

Pharmacotherapy of Aggression

Guidelines recommend psychosocial therapies as first-line treatment for aggression in young patients, followed by medications targeted toward the primary underlying disorder. Atypical antipsychotics can be offered after these steps have failed, but polypharmacy should be avoided.

Impulsive aggression is generally reactive, unplanned, and overt. This type of aggression is more common in clinical settings and is more amenable to pharmacological and psychosocial interventions than planned aggression, which is more characteristic of delinquent youth. The most common conditions underlying impulsive aggression are ADHD and disruptive behavior disorders such as conduct disorder or oppositional defiant disorder. Other less common underlying conditions are mood disorders, neurodevelopmental disorders, PTSD, autism spectrum disorders, and intellectual disability.

In young people with ADHD with or without comorbid disruptive behavior disorders, stimulants have been shown to improve aggression. However, they may not adequately control aggression in many patients, and aggression may reappear due to the drugs' short duration of action. Nonstimulant ADHD medications—atomoxetine and the long-acting α -2 adrenergic agonists clonidine and guanfacine—have more lasting effects on ADHD core symptoms but have not been compared directly to stimulants with regard to aggression, although they are often prescribed for this purpose. Atypical antipsychotics can also be effective when prescribed as adjuncts to ADHD agents, although they do not have FDA approval for this purpose. Mood stabilizers have long been prescribed to control aggression in patients with aggressive conduct disorders.

Behavioral problems and aggression often co-occur with depression and other mood disorders in young patients. Treatment with SSRIs can lead to reduced aggression in children with depression, as long as there is not a longstanding behavioral problem. However, SSRIs and other antidepressants are not recommended for aggression in children or adolescents in the absence of depression. Several studies indicate divalproex reduces aggression in children with bipolar mania; less evidence exists for other anticonvulsants. Lithium is approved for use in adolescents with bipolar disorder, and much anecdotal evidence suggests it is effective for aggression. Several atypical antipsychotics are approved for bipolar disorder in young people; quetiapine and risperidone have particular efficacy against aggression.

For children with autism or intellectual disability, atypical antipsychotics were often prescribed off-label for aggression. Recently risperidone and aripiprazole have demonstrated efficacy in clinical trials and are now FDA approved for this indication. Other, unapproved atypicals

appear to have similar efficacy. Beta-blockers are often prescribed off-label in these children but have not been evaluated in randomized controlled trials. Nonstimulant ADHD medications, such as clonidine and guanfacine, may be effective, particularly if a child has hyperactivity/impulsivity and sleep problems.

Regardless of the underlying or co-occurring conditions, medication for aggression should be used with close patient monitoring. Growth impairment and cardiovascular risk have been extensively debated but do not appear to be major concerns. Obtaining a baseline ECG is suggested only for patients with risk factors. Patients receiving atomoxetine or antidepressants should be monitored for suicide risk. First-generation antipsychotics are associated with extrapyramidal effects, and atypicals may induce weight gain, metabolic syndrome, and hyperprolactinemia.

Gurnani T, Ivanov I, Newcorn J: Pharmacotherapy of aggression in child and adolescent psychiatric disorders. *Journal of Child and Adolescent Psychopharmacology* 2016;26 (February):65–73. From Mount Sinai-St. Luke's Hospital Center; and the Icahn School of Medicine at Mount Sinai, NY. Source of funding not stated. Two study authors disclosed relationships with commercial sources; the third author declared no competing interests.

Common Drug Trade Names: aripiprazole—*Abilify*; atomoxetine—*Strattera*; clonidine—*Catapres*; divalproex—*Depakene, Depakote*; guanfacine—*Intuniv, Tenex*; quetiapine—*Seroquel*; risperidone—*Risperdal*

Childhood Trauma and Bipolar Disorder

Recent research has clarified the relationship between childhood trauma and bipolar disorder, but guidelines for applying this knowledge in clinical practice are lacking, according to an updated literature review.

Previous reviews of childhood trauma and bipolar disorder were published between 2008 and 2011. The present review, which includes a considerable amount of more recently published research, suggests that each of the 3 subtypes of childhood trauma—emotional, physical, and sexual—is associated with bipolar disorder, although the specific role of each type remains controversial.

The literature shows a consistent association between childhood trauma and several severe clinical characteristics of bipolar disorder: early onset, suicide attempts, and comorbid substance abuse. Associations with other severe characteristics—rapid cycling, psychotic features, and a higher number of lifetime mood episodes—have been shown less consistently. It appears that associations with more severe disease characteristics are driven by strong linkages in girls, with weaker associations in boys. Of the subtypes of trauma, physical and sexual abuse are the most frequently studied, but some research suggests emotional abuse and neglect may be specific risk factors for bipolar disorder.

In patients with bipolar disorder, childhood trauma is linked with increased emotional lability, increased aggression, and cognitive impairment. These deficits may increase vulnerability to other stressors such as cannabis exposure or life events in adulthood. Biological mechanisms, such as neuroplasticity, sleep deficits, and hypothalamic-pituitary-adrenal (HPA) axis function, further complicate the picture.

Childhood trauma should be investigated in all children with established or suspected bipolar disorder because it signals increased risk of a more severe illness over time. Assessment is especially indicated in patients with early-disease onset; suicide attempts; substance abuse; a high number of mood recurrences; or rapid cycling or other manifestations of mood instability. Numerous structured questionnaires have been developed for this purpose. While no particular assessment is recommended over any of the others, the Childhood Trauma Questionnaire is widely used in research and explores many types of trauma.

Evidence-based recommendations for managing trauma in children with bipolar disorder do not yet exist. However, trauma can be addressed with early intervention approaches such as coping strategies, body awareness/mindfulness techniques, and stress management. Studies in patients with established bipolar disorder are sparse, but do include some evidence in favor of eye movement desensitization and reprocessing and of cognitive behavioral therapy for sexually abused children. Therapies that specifically target emotional regulation or cognitive functioning might help counterbalance the effects of trauma.

Aas M, Henry C, Andreassen O, Bellivier F, et al: The role of childhood trauma in bipolar disorders. *International Journal of Bipolar Disorders* 2016; doi 10.1186/s40345-015-0042-0. From the University of Oslo, Norway; and other institutions. **Funded by Institut national de la santé et de la recherche médicale (INSERM); and other sources. The authors declared no competing interests.**

Brief CBT for Adolescent Depression

Treatment with brief cognitive behavioral therapy had small-to-moderate benefits in a group of adolescents with depression who declined antidepressant medication.

Methods: The investigators used an HMO's electronic medical records to identify primary-care patients, aged 12–18 years, who received a diagnosis of major depression and were given a prescription for an antidepressant but either did not fill the prescription or did not refill after the first 30 days. The study excluded patients with bipolar disorder, psychosis, mental retardation, or autism but included those with any other psychiatric comorbidity. Patients were randomly assigned to self-selected treatment as usual (TAU), with or without CBT. The CBT protocol consisted of 2 units, each with 4 individual sessions. The units covered cognitive therapy to address unrealistic thinking and behavioral activation to increase pleasant activities. The units could be completed in either order, and patients who recovered after a single unit were not required to complete the second. Up to 6 elective continuation contacts were permitted. Patients were assessed at 6, 12, and 26 weeks, and then at half-year intervals up to 2 years. The primary study outcome, depression recovery, was measured with the Longitudinal Interval Follow-up Evaluation and defined as ≥ 8 weeks with no or minimal symptoms and little or no impairment.

Results: A total of 212 adolescents were randomized to treatment. Use of TAU options during the 104 weeks of follow-up was high and similar in the 2 groups, with more than half of patients receiving outpatient mental health services, 30–36% receiving school counseling, and 18–32% receiving antidepressants or other psychotropic medication. Fewer CBT patients received inpatient treatment during follow-up: 5% versus 11%.

The majority of patients in both groups recovered from depression. Young people who received CBT had significantly higher rates of recovery than those who did not. (See table.) The peak difference between the 2 groups was greatest at 15–20 weeks. The average number needed to treat (NNT)* was 6 for recovery immediately post-treatment and 10 during the second year of follow-up. Secondary outcome measures of depression symptoms also favored CBT, but other secondary measures, such as treatment satisfaction, substance use, and suicidal behavior, did not differ between treatments.

Response and Recovery Rates			
	CBT plus TAU	TAU	Significance
Diagnostic Response			
Week 52	91%	88%	p=0.03
Week 104	94%	92%	p=0.03
Diagnostic Recovery			
Week 52	80%	69%	p=0.005
Week 104	89%	79%	p=0.003

Discussion: Previous research shows a majority of adolescents with depression decline antidepressant medication or are non-adherent in primary-care settings. In the present study CBT was associated with modest effects and high NNTs, and many of the benefits over TAU were transient. Nevertheless, even temporary relief of symptoms for 1 year can have clinical and developmental benefits in this age group.

Clarke G, DeBar L, Pearson J, Dickerson J, et al: Cognitive behavioral therapy in primary care for youth declining antidepressants: a randomized trial. *Pediatrics* 2016; doi 10.1542/peds.2015-1851. From Kaiser Permanente Center for Health Research, Portland, OR. Funded by the NIH. The authors declared no competing interests.

*See Reference Guide.

Tourette Syndrome in Children with ADHD

There is a misperception that stimulants are contraindicated in patients with tic disorders because of their potential to cause or exacerbate tics. ADHD and Tourette syndrome (TS) are highly comorbid, with nearly 65% of young patients with TS also affected by ADHD. Although tics can present as an adverse effect of stimulants, given the high comorbidity of the disorders, emerging tics can be a symptom of TS, which typically manifests at a later age than ADHD. Stimulants remain an important option for treatment in these children as they can reduce tic severity and improve quality of life.

The authors describe 2 children, aged 8 and 10 years, with ADHD in whom tics developed after successful stimulant treatment. Both children eventually received a diagnosis of TS and received treatment with dexamethylphenidate plus either clonidine or risperidone. Both children experienced relief from ADHD and the majority of tic symptoms.

Few of the medications commonly used for tic disorders in children are FDA approved for that indication. The authors recommend starting with a nonstimulant, such as clonidine or guanfacine, particularly the newer long-acting guanfacine formulations approved for ADHD. These agents can relieve both ADHD and tic symptoms. Recent evidence indicates that stimulants can be used in children with TS without worsening tics and that a combination of methylphenidate-clonidine is effective. Second-generation antipsychotics are an additional option for treating tics, although close monitoring is needed for metabolic, endocrine, extrapyramidal, and other side effects. First-generation neuroleptics are highly effective for tic disorders but remain a second-line option.

Oluwabusi O, Parke S, Ambrosini P: Tourette syndrome associated with attention deficit hyperactivity disorder: the impact of tics and psychopharmacological treatment options. *World Journal of Clinical Pediatrics* 2016;5 (February 8): 128-135. From Drexel University College of Medicine, Philadelphia, PA; and Yale School of Medicine, New Haven, CT. Source of funding not stated. The authors declared no competing interests.

Common Drug Trade Names: clonidine—*Catapres*; dexamethylphenidate—*Focalin*; guanfacine ER—*Intunivo*; methylphenidate—*Ritalin*; risperidone—*Risperdal*

Stimulants in ADHD with DMDD

Dose optimization of stimulants led to moderate-to-large improvements in problem behaviors in children with comorbid ADHD and disruptive mood dysregulation disorder.¹

Background: Children with ADHD and persistent irritability are increasingly being given mood stabilizers and atypical antipsychotics, despite concerns about these agents' use in young patients. It is unclear whether the best treatment for these children is stimulants and behavioral therapy targeting the externalizing symptoms or mood stabilizers and antipsychotics targeting irritability and aggression.

Methods: Stimulant dose optimization was carried out as part of a larger study of a psychosocial treatment for comorbid ADHD and DMDD in 68 children, aged 7-12 years.² Before psychosocial treatment, physicians assessed each child's stimulant dosage and, if indicated, started and/or optimized the drug over a 6-week period. The subjects of the present report were 38

children who had stimulants started or adjusted and who continued to meet diagnostic criteria for DMDD. Efficacy of stimulant treatment was measured as change from baseline to week 6 in various measures of mood symptoms, disruptive behavior, ADHD symptoms, and function.

Results: A total of 11 children were switched from 1 class of stimulants to another, usually at a lower dose equivalent; 11 had a dosage change within the same class, and 16 were previously stimulant naive. Baseline mood ratings suggested mild-to-moderate manic-like and depressive symptoms. Stimulant optimization was associated with significant improvement in mood and depression (see table), but changes from baseline in the Young Mania Rating Scale were not statistically significant. Parent ratings for behavioral symptoms showed moderate baseline levels of ADHD and oppositional defiant disorder (ODD) symptoms as well as mild conduct disorder (CD) symptoms; all improved after dose optimization (see table), as did some but not all teacher symptom ratings. Clinician-rated and parent-rated functioning also showed improvement over the course of the study, mostly with moderate effect sizes.* (See table.) Larger improvements in parent-rated ADHD and ODD were observed in treatment-naive patients versus those already taking stimulants; however, effects were similar in the 2 groups for teacher ratings. Medication was well tolerated, with most adverse effects decreasing over the period of observation.

Mean mood, behavioral, and ADHD symptom scores before and after stimulant optimization				
Measure	Baseline	Endpoint	Significance	Effect Size
Mood Severity Index	24.2	21	p<0.001	0.55
Children's Depression Rating Scale-Revised	34.3	30.9	p<0.001	0.61
Disruptive Behavior Disorders Rating Scale for ADHD	35.2	26.3	p<0.001	0.95
Disruptive Behavior Disorders Rating Scale for ODD	14.5	11.9	p<0.001	0.50
Disruptive Behavior Disorders Rating Scale for CD	5.3	3.3	p<0.001	0.65
Children's Global Assessment Scale	54.6	56.8	p=0.03	—

Discussion: The present study results suggest that stimulants may be a reasonable first-line option for patients with comorbid ADHD and DMDD. It should be noted that escalating to the maximum tolerable dose of a stimulant was less effective than switching to a lower dose of a different agent. However, residual impairment indicates that additional treatment is needed to optimize functioning.

¹Baweja R, Belin P, Humphrey H, Babocsai L, et al: The effectiveness and tolerability of central nervous system stimulants in school-age children with attention-deficit/hyperactivity disorder and disruptive mood dysregulation disorder across home and school. *Journal of Child and Adolescent Psychopharmacology* 2016;26 (March):154–163. From Penn State University College of Medicine, Hershey; and other institutions. **Funded by the NIMH. Two study authors disclosed financial relationships with commercial sources; the remaining 9 authors declared no competing interests.**

²Waxmonsky J, et al: A randomized clinical trial of an integrative group therapy for children with severe mood dysregulation. *Journal of the American Academy of Child and Adolescent Psychiatry* 2016;55 (March):196–207. See *Child & Adolescent Psychiatry Alerts* 2016;18 (April):22–23.

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.

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

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CHILD & ADOLESCENT PSYCHIATRY ALERTS

Adolescent ADHD Treatments.....	31
Antidepressants and Fracture Risk.....	35
Atomoxetine and Risk of Suicide	33
Autism: Potential Biomarker.....	32
Reference Guide	36
Suicide Prevention Interventions	34

Volume XVIII / June 2016 / Number 6

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Evidence-Based Treatment for Adolescent ADHD

Practice guidelines for ADHD are in large part based on research carried out in children or mixed-age groups. To determine if adolescent-specific issues, such as substance use and treatment adherence, make this extrapolation inappropriate, a systematic review of adolescent-only studies was conducted.

Methods: A comprehensive literature search identified all randomized, controlled trials of pharmacotherapy or psychosocial treatment conducted in patients with a DSM diagnosis of ADHD, using ≥ 1 valid outcome measure for ADHD symptoms or related functioning. Studies were included in the analysis only if they were carried out in patients aged 12–18 years, or if results were reported separately for this age group. Pharmacological treatments consisted of extended-release medications FDA-approved for pediatric ADHD. Psychosocial treatments included behavioral therapy, skills training, and cognitive behavioral therapy.

Results: From a total of >1300 identified ADHD clinical trials, only 17 were conducted in adolescents or presented results for this population separately: 6 randomized controlled trials and 1 meta-analysis of pharmacological treatments and 10 trials of psychosocial treatments, encompassing a total of 2668 patients. Both osmotic-release oral system (OROS) and transdermal methylphenidate, as well as extended-release amphetamine–dextroamphetamine and lisdexamfetamine, were significantly superior to placebo at reducing core ADHD symptoms. OROS methylphenidate was associated with a 47% mean reduction in the ADHD Rating Scale (ADHD-RS) total score, compared with a 31% reduction with placebo ($p=0.001$). Transdermal methylphenidate was associated with a nearly 10-point greater reduction in symptom scores than placebo. There were no randomized controlled trials of dexamethylphenidate in adolescents. Extended-release amphetamine–dextroamphetamine showed an 18-point improvement in the ADHD-RS total symptom score relative to 9 for placebo ($p<0.001$), with greater effect on hyperactive-impulsive symptoms than inattentive symptoms. Lisdexamfetamine was associated with greater reductions in the ADHD-RS than placebo (18–21 points for different dosages, vs. 13 points for placebo; $p<0.006$). Atomoxetine was also found to be superior to placebo,

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while evidence for the other non-stimulant medications, guanfacine, and clonidine was limited or absent for adolescents.

Psychosocial treatments were investigated in a total of 916 participants in 10 trials, all using multicomponent interventions targeting functional outcomes. Most studies were rated poorly on quality measures such as blinding and small sample sizes. Effects of treatment on core ADHD symptoms, emotional and behavioral symptoms, and academic performance were inconsistent. Five studies showed that psychosocial therapies were associated with medium-to-large effects on organizational skills or executive functioning. Effects on overall functioning and impairment were modest at best.

Discussion: While the results of this review support current clinical guidelines, they also highlight the lack of high-quality research in adolescent-only populations. In addition, the review did not attempt to address several important aspects of ADHD treatment in adolescents such as concerns of addiction to stimulant medications, stimulant misuse, and the potential risk of developing substance-use disorders. These, along with potential mediators and moderators of treatment effects, require additional study.

Study Rating*—16 (89%): This study met most criteria for a systematic review; however, the source of funding was not stated.

Chan E, Fogler J, Hammerness P: Treatment of attention-deficit/hyperactivity disorder in adolescents: a systematic review. *JAMA* 2016;315 (May 10):1997–2008. From Boston Children's Hospital and Harvard Medical School, MA. **Source of funding not stated. Two of the 3 study authors disclosed financial relationships with commercial sources.**

Common Drug Trade Names: atomoxetine—*Strattera*; clonidine—*Catapres*; dexamethylphenidate—*Focalin*; amphetamine-dextroamphetamine, extended-release—*Adderall XR*; guanfacine—*Intuniv*; lisdexamfetamine—*Vyvanse*; OROS methylphenidate—*Concerta*; transdermal methylphenidate—*Daytrana*

*See Reference Guide.

Salivary Marker for Autism

In a preliminary study, 14 micro RNA (miRNA)-based salivary biomarkers accurately distinguished children with autism spectrum disorder (ASD) from those without. These markers, which can be measured at any time after birth, had nearly twice the specificity* of the screening questionnaire that is currently the gold standard for identifying ASD in early childhood.

Background: Biomarker screening is an attractive approach to ASD, but nearly 2000 genes have been implicated in the disorder. MiRNA may offer a more targeted approach via its mechanism of epigenetic regulation: Cells can influence the genetic expression of other cells by extruding miRNA into the extracellular space, from which it enters neighboring cells and blocks synthesis of target proteins by messenger RNA. The extracellular nature of this process allows genetic material from the CNS to be measured in bodily fluids including saliva.

Methods: Saliva samples were obtained during well-child visits from 24 children, aged 4–14 years, with a DSM-5 diagnosis of ASD, excluding those with syndromic phenotypes such as fragile X. Samples were also obtained from 21 healthy comparison children without ASD. Those with ASD had mild-to-moderate symptoms as measured by the Autism Diagnosis Observation Schedule, and deficits in Communication, Social Interaction, and Activities of Daily Living on the Vineland Adaptive Behavior Scales. Both patient and control groups included children with comorbid diagnoses, predominantly ADHD.

Results: A total of 246 miRNAs were identifiable in at least half of the samples, regardless of diagnosis. Among these, 14 miRNAs showed significant differences between children with and without ASD. A model based on this set of miRNAs correctly identified 100% of patients with ASD (sensitivity*) and excluded 96% of those without the disorder (specificity). The researchers

then identified target messenger RNAs for each miRNA and compared the target genes with a database of candidate autism genes, finding an overlap that was 2.2-fold greater than chance. Targets of the marker miRNAs were associated with neurodevelopmental processes and functions relevant to ASD. As a final step, the investigators examined a publicly available database of the distribution of miRNAs across the developing human brain from ages 4 months to 23 years. The markers were expressed in multiple brain regions throughout childhood.

Discussion: Current ASD screening is based on parent questionnaires such as the Modified Checklist for Autism in Toddlers-Revised, a test that cannot be administered until the child is aged 16–30 months and even then has a false-positive rate of 50%. Adding saliva-based biomarker testing could lower the age of diagnosis and early intervention and reduce the burden of treating children who do not have ASD. The miRNA biomarkers, if validated in a larger population and in younger children, may be ideal biomarkers for ASD.

Hicks S, Ignacio C, Gentile K, Middleton F: Salivary miRNA profiles identify children with autism spectrum disorder, correlate with adaptive behavior, and implicate ASD candidate genes involved in neurodevelopment. *BMC Pediatrics* 2016; doi 10.1186/s12887-016-0586-x. From the State University of New York (SUNY) Upstate Medical University, Syracuse. Funded by SUNY; and the American Academy of Pediatrics. The authors declared no competing interests.

*See Reference Guide.

Atomoxetine and Suicide Risk

In a population-based study of children and adolescents, atomoxetine (*Strattera*) was not associated with increased risk of suicidal behavior.¹ This observation contradicts the drug's boxed warning of increased risk in young patients with ADHD, which was based on a meta-analysis of clinical-trial data.²

Methods: Medicaid claims data from 26 states were examined between 2002 and 2006 to identify patients, aged 5–18 years, with new prescriptions for atomoxetine or stimulants. Although atomoxetine was not considered first-line therapy for ADHD at the time, about half of new prescriptions were in medication-naive patients. Therefore, separate analyses were conducted for patients receiving either type of drug as first-line therapy and for patients receiving second-line treatment with a stimulant augmented with either atomoxetine or a second stimulant. The primary study endpoint was completed suicide or suicide attempt requiring hospitalization or emergency care. Results were adjusted using propensity scores* estimating the likelihood of receiving atomoxetine.

Results: The analysis of first-line treatment included nearly 300,000 patients, of whom about 20% had a prescription for atomoxetine. The analysis of second-line treatment included >220,000 patients, of whom 26% received atomoxetine. A total of 140 suicide attempts were observed with first-line therapy and 90 with second-line therapy. Adjusted hazard ratios* showed no difference in the rate of suicide events between patients currently receiving atomoxetine or stimulants. (See table.) Event rates did not differ between groups at any of the evaluation points: 3 months, 6 months, 24 months, or for all available follow-up.

Suicidal behavior in the first year of follow-up during administration of atomoxetine or stimulants			
	Atomoxetine	Stimulants	Adjusted Hazard Ratio
<i>First-Line Therapy</i>			
Number of suicidal events	18	50	0.95
<i>Second-Line Therapy</i>			
Number of suicidal events	11	46	0.71

Discussion: Most of the atomoxetine exposure in the present study occurred before there was much concern over suicidality, which suggests the drug was not being channeled to patients with lower suicide risk. Patients who received atomoxetine were older, more likely to have substance use problems, and had more depression and oppositional defiant disorder than those receiving stimulants—all risk factors for suicide. Wide confidence intervals did not permit the investigators to examine suicidal behavior in high-risk groups or over long periods of time, but any excess risks are likely to be small.

¹Linden S, Bussing R, Kubilis P, Gerhard T, et al: Risk of suicidal events with atomoxetine compared to stimulant treatment: a cohort study. *Pediatrics* 2016;137(5):e20153199. From the University of Florida, Gainesville; and Rutgers University, New Brunswick, NJ. **Funded by the National Health and Medical Research Council; and other sources. The authors declared no competing interests.**

²Bangs M, et al. Meta-analysis of suicide-related behavior events in patients treated with atomoxetine. *Journal of the American Academy of Child Adolescent Psychiatry* 2008;47(2):209–218.

*See Reference Guide.

Suicide Prevention Interventions

According to results of a systematic review, there are a variety of effective psychosocial interventions for youth suicide prevention that can be offered in school, community, and healthcare settings.

Methods: The review included published studies comparing psychosocial suicide prevention interventions with a control condition—i.e., treatment as usual, a waiting list, attention, or no treatment. Study populations were adolescents or young adults, aged 12–25 years, and study outcomes were deliberate self-harm and suicidal ideation, plans, or attempts.

Results: The search identified 28 studies that evaluated 32 comparisons in >10,600 participants. In 22 of the trials, the intervention was provided to patients with a history of suicidal ideation or an attempt; 8 trials selected patients with a history of depression and/or deliberate self-harm, and 2 studies recruited patients with no formal diagnosis. Participants had a median age of 16 years and were recruited from schools, inpatient facilities, outpatient clinics, emergency departments, universities, and primary-care settings. Interventions studied were social support (37%), cognitive behavioral therapy (25%), problem-solving therapy (22%), motivational interviewing (22%), psychoeducation (13%), and dialectical behavior therapy (9%). Several trials evaluated >1 active intervention.

Overall, 17 (53%) trials reported a significant positive effect of the intervention on the suicidal outcome. Of these effective programs, 6 were delivered in the school environment, 3 were community based, and 8 were delivered in a health-care setting (see box); results were comparable in different settings. About half of

Suicide Prevention Programs Effective in Adolescents	
Program	Significantly Improved Outcome
School-Based Programs	
Counselors Care, Assess, Respond, Empower (C-CARE)	Suicidal ideation
Parents CARE (P-CARE)	Suicidal ideation
Intensive Psychotherapy for Depressed Adolescents with Suicidal Risk	Suicidal ideation
Coping and Support Training	Suicidal ideation
Signs of Suicide	Suicide attempt
Community-Based Programs	
Youth-Nominated Support Team	Suicidal ideation
Multisystemic Therapy	Suicidal attempt
Problem-Solving Therapy	Suicidal ideation
Healthcare Setting-Based Programs	
Dialectical Behavior Therapy for Adolescents	Suicidal ideation, deliberate self-harm
Resourceful Adolescent Parent Program	Suicidality
Attachment-Based Family Therapy	Suicidal ideation
Interpersonal Therapy	Self-harm
Mentalization-Based Treatment for Adolescents	Deliberate self-harm
Cognitive Behavioral Therapy	Suicidal ideation
Problem-Solving Therapy	Suicidal ideation
Developmental Group Psychotherapy	Repeated self-harm

programs that offered a traditional psychotherapeutic approach were effective, as were half of those with a less formal type of intervention. Both of the universally delivered programs reported significant effects on suicide attempts. Half of the selectively delivered programs and half of the programs delivered to an indicated population were effective. Most of the combined individual and parent/family programs were effective, as were about half of the programs that were group-based, combined individual and group-based, individually delivered, or parent- or family-targeted.

Discussion: Overall, about half of the programs identified in the review had significant effects on suicidal ideation, suicide attempts, or self-harm. The effects ranged from small to large and were evident in both the short and long term. Several programs showed positive effects that did not reach statistical significance, possibly because the studies were small and underpowered.

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

Calear A, Christensen H, Freeman A, Fenton K, et al: A systematic review of psychosocial suicide prevention interventions for youth. *European Child and Adolescent Psychiatry* 2016;25 (May):467–482. From the National Institute for Mental Health Research, Australia; and other institutions. **Funded by the National Health and Medical Research Council. The authors declared no competing interests.**

*See Reference Guide.

Antidepressants and Fracture Risk

According to results of a retrospective cohort study, antidepressant use appears to be associated with a small but significant increase in risk of fracture, particularly during the first month of treatment.

Background: SSRIs have been linked to bone loss and increased fracture risk in adults, but little is known about these effects in childhood or adolescence, a crucial time in skeletal development. Negative effects on bone formation and remodeling could place young people at risk for poor bone quality, growth, strength, and density.

Methods: Ohio Medicaid claims data were used to identify a study cohort of patients, aged 6–17 years ($n=50,673$), who experienced a new episode of depression between July 2001 and June 2009. Youth who had experienced a fracture in the 6 months prior to antidepressant initiation or who had received antidepressant therapy within the 6 months prior to depression diagnosis were excluded. Fractures were compared over a median of 1.7 years of follow-up between patients who did ($n=17,691$) and did not ($n=32,982$) receive antidepressant therapy.

Results: A total of 5872 fractures occurred during follow-up. Compared with no antidepressant use, current antidepressant use was associated with a slight but significantly elevated incidence of fracture (38% vs. 35%; hazard ratio,* 1.03; $p=0.03$). The increase was associated with all classes of antidepressants (i.e., SSRIs, TCAs, others) and with all individual antidepressants examined except for fluoxetine and duloxetine. Adjusted incidence rates were 44 per 10,000 patients in the first 30 days of antidepressant therapy, compared with 19–28 per 10,000 patients in subsequent months (risk ratio,* 2.0; $p=0.007$). Fracture incidence did not differ between youths with past antidepressant use and those who never received treatment.

Discussion: Increased fracture risk early in antidepressant treatment may be associated with a greater propensity for falls, behavioral disinhibition that could increase risk of trauma, or anticholinergic or cardiovascular effects on postural stability. Regardless of the mechanism, which could not be evaluated with the present study design, these results highlight the need to proactively reduce antidepressant-associated fracture risk, particularly on initiation or with a change in antidepressant class. Strategies to reduce risk include close monitoring for

adverse effects and/or concomitant conditions that could affect fall risk; evaluating orthostatic blood pressure and pulse; assessing gait and balance; and reviewing nutrition, activity levels, and concurrent medications. Weight-bearing exercise, along with adequate dietary vitamin-D and calcium intake, could improve bone strength in patients with underlying fracture risk.

Gracious B, Fontanella C, Phillips G, Bridge J, et al: Antidepressant exposure and risk of fracture among Medicaid-covered youth. *Journal of Clinical Psychiatry* 2016; doi 10.4088/JCP.15m09828. From The Ohio State University, Columbus; and other institutions. **Funded by the National Center for Research Resources; and other sources. The authors declared no competing interests.**

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

*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.

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

Risk Ratio: 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.

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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ADHD: Neural and Genetic Correlates	37
Antidepressants: Relative Efficacy	40
Antipsychotics: Cardiac Safety	39
Methylphenidate: Cardiac Safety	38
Puberty and Depression Risk.....	41
Reference Guide	42

Volume XVIII / July 2016 / Number 7

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Neural and Genetic Correlates of ADHD

Over the past 2 decades, substantial research using new technologies has been focused on investigating neurologic and genetic associations of ADHD. New brain-imaging approaches have led to the description of alterations in brain anatomy and circuitry associated with the disorder. In genetics, endophenotypes (distinct heritable traits that reflect genetic influences more closely than the disorder itself) are an expanding focus of research. Which of these neural and genetic associations are causal, rather than adaptations to the disorder, remains to be established. Development of new interventions and preventive strategies will rely on identifying pathways of causation from genes to neural circuits to behavior.

Neuroimaging studies have implicated several large-scale neural circuits in ADHD, particularly those related to sustained attention, inhibitory control, motivation, and emotional regulation. Structural MRI studies have consistently identified volumetric reductions in the basal ganglia, which are important to goal-directed behaviors, motivation/reward processing, and motor control—all impaired in persons with ADHD. These alterations lessen as the individual develops and are no longer detectable by adulthood, suggesting that ADHD may be a disorder of delayed maturation. Structural MRI has also identified abnormalities in frontal and parietotemporal cortical thickness in ADHD. Delays in reaching peak cortical thickness in children with ADHD also support the hypothesis of delayed maturation.

Connectivity analyses have been carried out using data from diffusion MRI (dMRI) and from testing of both resting-state and task-based functional connectivity. dMRI studies have identified deficits in white matter organization in dorsal frontostriatal and frontoparietal circuits and mesocorticolimbic circuits that might be related to deficits in motivation. These findings complement structural MRI studies in that the affected white matter tracts connect regions with volumetric abnormalities. Resting state functional connectivity studies have identified reduced connectivity within the default mode network (DMN), which may underlie self-referential cognitions, introspection, and mind-wandering. Persons with ADHD may have difficulty deactivating the DMN when turning to tasks that require attention. The DMN normally works in

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opposition to the cognitive control network, which is involved in executive functions. However, persons with ADHD may lack the normal inverse correlation between activity of these 2 networks. Task-based functional MRI studies show deficits in regions associated with inhibitory control and reward processing. Taken together, all of these different MRI studies implicate a consistent set of neural circuits related to attentional processes and inhibitory control, sustained attention, and motivation.

Genetic studies of ADHD have examined single candidate risk genes, genome-wide associations, rare chromosomal abnormalities known as copy number variants, and polygenic risk scores. Given the difficulty of linking genes to the diagnosis, attention has turned to endophenotypes—distinct heritable traits that lie on the path between genes and disorder. Endophenotypes may be more proximal to genetic influence than the disorder itself and more amenable to investigation. Candidate endophenotypes in ADHD include intra-individual reaction-time variability, response inhibition, and deficits in working memory. Whether specific abnormalities in neural circuits are related to cognitive endophenotypes remains to be seen.

Gallo E, Posner J: Moving towards causality in attention-deficit hyperactivity disorder: overview of neural and genetic mechanisms. *Lancet Psychiatry* 2016;3 (June):555–567. From Columbia University and the New York State Psychiatric Institute. **Funded by the NIH; and the Edwin S. Webster Foundation. One study author disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

Cardiovascular Safety of Methylphenidate

Use of methylphenidate (*Ritalin*) in children and adolescents is associated with increased risk of cardiac arrhythmia and myocardial infarction (MI), according to results of a population-based study. However, these events are uncommon and the absolute risk is likely to be low. There does not appear to be increased risk of other cardiovascular events.

Methods: Claims data were analyzed from South Korea's national health insurance system for patients aged ≤ 17 years who had a diagnosis of ADHD. Methylphenidate prescriptions and the occurrence of cardiovascular events occurring in 2008–2011 were recorded. Each participant served as his or her own control, and the occurrence of cardiovascular events during each patient's time exposed or unexposed to methylphenidate was compared. Methylphenidate exposure was divided into periods of 1–3 days, 4–7 days, 8–14 days, 15–28 days, 29–56 days, and >56 days. The analysis was adjusted for time-varying confounders, including age, comorbidities, and exposure to other psychoactive drugs.

Results: Of $>144,000$ children and adolescents with ADHD identified, about 114,600 received a new prescription for methylphenidate during the study period. A total of 1224 of these patients experienced a cardiovascular event: arrhythmias ($n=864$), hypertension ($n=396$), MI ($n=52$), stroke ($n=67$), and heart failure ($n=44$). The median age at first methylphenidate exposure was 11–13 years, as was the median age at first cardiovascular event.

The incidence of arrhythmia was increased during methylphenidate exposure of any duration (adjusted incidence rate ratio [IRR],* 1.61). The highest risk was during the first 3 days of treatment; and risk returned to baseline levels after 56 days. Arrhythmia risk was higher during methylphenidate use in children with congenital heart disease (IRR, 3.49), but the incidence remained elevated in those without congenital heart disease.

Methylphenidate was not associated with hypertension overall, but risk was increased in the first week after the start of methylphenidate treatment (IRR, 1.29). MI risk was not elevated overall, but there was about a 2-fold increase in risk after the first week of treatment, lasting through the 56-day period and then diminishing. Methylphenidate was not associated with increased risk of stroke or heart failure.

Discussion: Previous studies have reported no association of methylphenidate with cardiovascular adverse events, but they may have lacked sufficient statistical power, given the rare occurrence of these events. The present study had an adequate sample size and was also able to produce risk estimates for different time periods. The results of this analysis are consistent with the biological mechanisms of these effects: immediate onset with arrhythmia and delayed onset with MI.

Shin J-Y, Roughead E, Park B-J, Pratt N: Cardiovascular safety of methylphenidate among children and young people with attention-deficit/hyperactivity disorder (ADHD): nationwide self controlled case series study. *BMJ* 2016; doi 10.1136/bmj.i2550. From Jewish General Hospital, Montreal, Canada; and other institutions. **This study was conducted without external funding. The study authors all declared no competing interests.**

*See Reference Guide.

Cardiac Safety of Antipsychotics

In a study in pediatric patients, QT interval and heart rate were not altered during the first year of treatment with the 3 most commonly prescribed second-generation antipsychotics.

Methods: Study participants (n=216) were children and adolescents who received treatment at 4 Spanish hospitals, either as outpatients or in short-term inpatient units. At their baseline visit, they were classified as either antipsychotic-naïve (with no prior treatment) or quasi-naïve (with their first prescription started within a month of study enrollment). The study included patients with any psychiatric disorder and those who received treatment concurrently with antidepressants, anticholinergics, mood stabilizers, or benzodiazepines. Electrocardiograms (ECGs) were performed at baseline and at 3-, 6-, and 12-month follow-up visits. For each patient, the corrected QT interval (QTc) was measured independently by 2 cardiologists. Because pathological levels of QTc are a matter of controversy, the authors chose a threshold, >440 milliseconds (ms), supported by recent pediatric cardiology literature.

Results: Of the 216 study patients, 137 received treatment with risperidone, 34 with olanzapine, 33 with quetiapine, and 2 with other drugs. Most patients (35%) had a diagnosis of schizophrenia, schizoaffective disorder, or other psychotic disorder, followed by mood disorder (27%) and ADHD/behavior disorder (19%). The average age was 14 years, and the youngest patient was age 4 years. Four patients (<2%) had a personal history of cardiac disease, and 45 (22%) had a family history. Patients who received risperidone were younger than the others on average and less likely to be given a prescription for an SSRI.

The mean baseline QTc was 396.74 ms. The average QTc did not change during the study, no patient had a QTc >500 ms, and no patient had treatment stopped because of QTc elevation. There were no differences in mean QTc among the 3 drugs, between treatment-naïve and quasi-naïve patients, or according to age, diagnosis, cumulative medication exposure, alcohol use, or cannabis use. Baseline QTc values were higher in girls and in patients taking antidepressants and were lower in overweight patients, but all of these differences narrowed and became statistically nonsignificant with time.

At baseline, 9 patients had QTc intervals above the 440-ms cutoff. Elevations were observed in 9 patients at 3 months, 6 patients at 6 months, and none at 12 months. These elevations were not associated with individual drugs, the cumulative dose, or other factors. Average heart rate tended to decrease with time in the sample.

Discussion: These results support the cardiac safety of atypical antipsychotics, previously shown in a small number of pediatric safety studies. This study did not confirm previous inconsistent reports of heart-rate increases in young patients taking atypicals, nor did it confirm any risk factors for QTc prolongation suggested by previous research. The naturalistic

study design suggests the results can be generalized to different treatment settings. The authors recommend restricting follow-up ECGs in patients taking the 3 study drugs to those with clinical cardiac risk factors or congenital or family history of heart disease, and possibly those who gain weight during treatment.

Alda J, Munoz-Samons D, Tor J, Merchan-Naranjo J, et al: Absence of change in corrected QT interval in children and adolescents receiving antipsychotic treatment: a 12 month study. *Journal of Child and Adolescent Psychopharmacology* 2016;26 (June):449–457. From the Hospital Sant Joan de Deu, Barcelona, Spain; and other institutions. **Funded by the Spanish Ministry of Economy and Competitiveness; and other sources. Six study authors disclosed financial relationships with commercial sources; the remaining 6 authors declared no competing interests.**

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

Relative Antidepressant Efficacy

According to results of a network meta-analysis* of all available clinical trials, fluoxetine appears to be the best option among available antidepressants for children and adolescents.

Background: Antidepressants have previously been compared in pairwise meta-analyses, but this study appears to be the first network meta-analysis, a type of analysis that allows indirect comparisons between drugs based on their effects relative to placebo or other common comparators.

Methods: A comprehensive literature search identified 34 published and unpublished parallel randomized controlled trials conducted through May 2015 that investigated any antidepressant for acute treatment. Participants had mean ages ranging from 9 to 18 years and had a primary diagnosis of major depressive disorder, according to standardized criteria. The primary efficacy outcome was change from baseline to study endpoint in depressive symptoms, measured using the clinician-rated Children's Depression Rating Scale–Revised, the Beck Depression Inventory, or the Children's Depression Inventory. Secondary outcomes included response ($\geq 50\%$ symptom reduction), all-cause discontinuation, and suicidal behavior or ideation.

Results: The 34 randomized trials assessed 14 different antidepressants and had a mean sample size of 159 patients. The trials included 5260 participants, of whom 2154 received placebo. Most trials were 8 weeks in duration and enrolled patients with moderate-to-severe depression. Most studies ($n=22$) were industry-sponsored; 4 trials were rated as low risk of bias, 20 as moderate risk, and 10 as high risk.

The largest number of trials were comparisons of fluoxetine with placebo. In the network meta-analysis, fluoxetine was statistically superior to placebo (standard mean difference,* 0.51) and to several other drugs for the primary outcome. No other drug was superior to placebo. Results for the secondary outcomes of response and all-cause discontinuation were similar and supported the results of the main analysis. Fluoxetine was also rated as the best drug in terms of tolerability. Venlafaxine was associated with a higher risk of suicidal behavior or ideation compared with placebo (odds ratio,* 0.13 in favor of placebo), and compared with 5 other antidepressants. Many antidepressants lacked reliable data on risk of suicidality.

Discussion: The moderate effect size of fluoxetine raises doubts about whether this result is robust enough to inform clinical practice. Estimates of tolerability are also not easily interpreted because of large confidence intervals, potential biases, and small numbers of studies. Notwithstanding these concerns, fluoxetine

Network Meta-Analysis Efficacy Ranking of Antidepressants

Fluoxetine
Desipramine
Duloxetine
Venlafaxine
Mirtazapine
Sertraline
Citalopram
Escitalopram
Paroxetine
Nefazodone
Imipramine
Amitriptyline
Clomipramine
Nortriptyline

may be considered the best drug option in children and adolescents with major depression. However, its use should be limited to those with moderate-to-severe depression who have not had response with nonpharmacologic therapy or those who lack access to psychotherapy.

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

Cipriani A, Zhou X, Del Giovane C, Hetrick S, et al: Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 2016; doi 10.1016/S0140-6736(16)30385-3. From the University of Oxford, U.K.; and other institutions. **Funded by the National Basic Research Program of China. Eight Study authors disclosed financial relationships with commercial sources; the remaining 11 authors declared no competing interests.**

Common Drug Trade Names: amitriptyline—*Elavil*; citalopram—*Celexa*; clomipramine—*Anafranil*; desipramine—*Norpramin*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; imipramine—*Tofranil*; mirtazapine—*Remeron*; nefazodone—*Serzone*; nortriptyline—*Pamelor*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor*

*See Reference Guide.

Early Puberty and Adolescent Depression Risk

In a population-based study, early breast development was associated with increased risk of depression in adolescent girls. Early puberty did not increase depression risk in boys.

Background: A Hong Kong-Chinese national birth cohort was initially assembled in 1997 to investigate the effects of secondhand tobacco smoke on infants. The cohort consisted of nearly all children born in Hong Kong in April or May 1997. The same cohort was used to assess the effects of age at puberty onset on depression.

Methods: Puberty onset was assessed by physicians using the Marshall and Tanner stages during ongoing biannual school health examinations beginning in grade 2 (ages 6–7 years). Puberty onset was defined as Tanner stage II for development of breasts in girls and genitalia in boys and for pubic-hair development in both genders. Depressive symptoms were assessed between 2010 and 2012 using the 9-item Patient Health Questionnaire, with depression defined as a total score of ≥ 11 points. The statistical analysis was adjusted for socioeconomic position (known to influence both puberty onset and depression), body mass index, and other factors.

Results: More than 5500 children were included in the analysis. Depression was assessed at an average age of 13.6 years. The mean age of breast-development onset was 9 years; genital development occurred at a mean age of 11 years, and age at pubic-hair onset was nearly 11 years for girls and nearly 12 years for boys. In girls, early breast development was associated with a higher risk of depression (fully adjusted odds ratio,* 0.83). This odds ratio corresponds to a 17% reduction in risk of adolescent depression for every 1-year delay in breast development. Depression risk was not associated with development of the genitalia in boys or with the appearance of pubic hair in either gender.

Discussion: Previous studies from Western countries have found early puberty onset to be associated with depressive symptoms in girls, but the studies did not examine the role of specific indicators. The effect of early puberty on depression may be attributable to biological and/or social phenomena. Estradiol plays a key role in breast development and may increase girls' sensitivity to negative psychological effects. Genital development in boys is driven by testosterone, and pubic-hair onset is a response to adrenal androgen production, hormones that may be emotionally neutral. Social context may play a role: Early puberty onset in girls can work against maintaining relationships and psychological well-being, but early puberty may increase status in boys. Whether the effects are sustained or transient remains to be seen.

Wang H, Lin S-L, Leung G, Schooling M: Age at onset of puberty and adolescent depression: "Children of 1997" birth cohort. *Pediatrics* 2016;137 (June):e20153231. From the University of Hong Kong, China; and City University of New York. **Funded by the Health and Health Services Research Fund. The authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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%.

Network Meta-Analysis: A study design that can provide estimates of efficacy for multiple treatment regimens 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.

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.

Standardized Mean Difference: The difference between 2 normalized means—i.e. the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales.

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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CHILD & ADOLESCENT PSYCHIATRY ALERTS

Anxiety Treatments.....	43
Computer Gaming for Autism.....	44
Conduct Disorder Pharmacotherapy.....	47
D-cycloserine for OCD.....	46
Energy Drinks and Mental Health.....	45
Parental Accommodation in Anxiety.....	48
Reference Guide.....	48

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Treating Anxiety Disorders

A stepped-care approach offers the greatest potential to effectively treat anxiety disorders in children and adolescents, according to an evidence-based review. Access to full cognitive behavioral therapy (CBT), the preferred treatment, is limited, but low-intensity therapist-supervised parent or electronic interventions can be effective. Medication should be reserved for the most intensive tier of treatment.

CBT has been far more extensively evaluated than any other treatment for pediatric anxiety disorders. A recent Cochrane review analyzed 26 studies in patients aged 4–18 years, although those aged <7 years were underrepresented. Most studies used a generic treatment approach rather than one tailored to a specific disorder. Nearly 60% of patients who received CBT achieved remission, compared with 18% of wait-listed controls, with a number needed to treat* of 3. The few studies with follow-up beyond the initial treatment found that remission rates increased in controls, and differences did not remain statistically significant. There have been no trials comparing CBT with a non-CBT active therapy; hence, there is no evidence that CBT is superior to any other psychological therapy. The recommendation in favor of CBT is based on the absence of robust evidence supporting any other treatment. A major challenge is to identify which children will be represented among the 40% who continue to have anxiety after completing CBT. Limited evidence suggests outcome is poorer in patients with social anxiety disorder or comorbid mood or externalizing disorders.

Numerous trials found pharmacotherapy with an SSRI or SNRI to be superior to placebo, but most of these trials were conducted in patients with obsessive-compulsive disorder (OCD), no longer considered an anxiety disorder in DSM-5. A single large study, the Child/Adolescent Anxiety Multimodal Study, found that sertraline (*Zoloft*) plus CBT was highly effective in non-OCD anxiety disorders. Outcomes were poorer in patients with higher initial anxiety severity, adolescents (vs. children), minorities, those with higher levels of caregiver strain, and those with social anxiety disorder.

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The high cost of CBT and limited availability of trained practitioners has led to innovations such as brief or low-intensity CBT that can be delivered by non-specialists. Brief parent-led, therapist-guided CBT has been evaluated primarily in preadolescent children and found to be effective. The few studies have shown response rates comparable to intensive CBT with only a few hours of therapist support. A recent review of 7 CBT-based electronic interventions, all with therapist support, found medium effect sizes in children and adolescents.

The authors recommend a stepped-care approach consisting sequentially of: 1) low-intensity intervention; 2) high-intensity CBT; 3) booster sessions in patients who have made good progress but have remaining problems; and 4) specialist assessment and consideration of pharmacotherapy.

Creswell C, Waite P: Recent developments in the treatment of anxiety disorders in children and adolescents. *Evidence Based Mental Health* 2016;19 (August):65–68. From the University of Reading, U.K. **Funded by the National Institute for Health Research. The authors declared no competing interests.**

*See Reference Guide.

Home-Based Gaming Platform for Autism

Results of a small pilot study in children with autism indicate that a computer gaming platform designed to address specific deficits in imitation and joint attention is a feasible and potentially useful intervention.

Background: Successful treatment in children with autism requires intensive intervention often involving ≥ 20 hours per week. This level of interaction is difficult to achieve for both patients' families and therapists. Computer-based programs have been shown to improve attention; fine motor skills; self-stimulatory behaviors; agitation; and perseverative responses in children with autism. The present study was undertaken to determine the feasibility of the computer-based game system Gaming Open Library Intervention for Autism at Home (GOLIAH), designed as a shared activity with parents or therapists. Also studied were its effects on imitation and joint attention, 2 important deficits in patients with autism.

Methods: In a 3-month open trial, GOLIAH was investigated in 10 boys, aged 5–9 years, with a confirmed diagnosis of autism. Participants played the games in 20-minute sessions: at home with a parent 5 times per week and at the hospital with a therapist once per week. The platform consists of games focusing on imitation and joint attention, with varying levels of difficulty, which can be selected by the therapist. Using separate hand-held tablets or computers, the games can be played at home with the parents, and also remotely with the therapist at scheduled times. The games have an automated evaluation process but are also evaluated manually by the parents, providing guidance for the therapist to monitor the child's progress and add or remove modules. The platform provides the therapist with metrics on the child's performance (e.g., speed and correctness) and other types of feedback (e.g., screenshots and audio recordings). Game modules are based on the Early Start Denver Model, a comprehensive, behavioral early-intervention model, and consist of 11 imitation or joint-attention games involving such tasks as imitating sounds, building or assembling objects, free drawing, or identifying objects pointed to by the adult.

Results: During the 3-month study period, parents and children participated in about 80% of the individual games. All of the children were able to go through all of the game levels, although not fully—given the diversity and level of difficulty within the games. Analysis of program metrics showed faster completion and a reduced number of errors over time in joint attention-focused games. Moreover, the imitation-focused game metrics indicated faster and improved quality of model reproductions. In a questionnaire, parents reported small improvements in tasks directly trained by the games, but more robust improvements in other

areas such as the child's self-esteem, concentration, and flexibility, and in the quality of the parent-child relationship.

Discussion: While these preliminary results are positive, they require replication. A larger study is currently underway in a more diverse patient sample and using validated external measures of imitation and joint attention. It should be noted that the GOLIAH platform is intended to enhance standard autism interventions, not to replace them.

Bono V, Narzisi A, Jouen A-L, Tilmont E, et al: GOLIAH: a gaming platform for home-based intervention in autism—principles and design. *Frontiers in Psychiatry* 2016; doi 10.3389/fpsy.2016.00070. From the University of Southampton, U.K.; and other institutions. **Funded by the European Commission; and other sources. The authors declared no competing interests.**

Energy Drinks and Mental Health

Evidence, although limited, suggests a link between energy-drink consumption and mental health. These products are aggressively marketed to young people, and as much as 30–50% of the adolescent/young adult population is known to consume energy drinks.

Energy drinks are caffeinated soft drinks that claim to boost performance and endurance, in contrast to sports drinks that profess to rehydrate and replenish electrolytes following exercise. The high caffeine content of energy drinks has been cause for concern. These drinks may also contain herbal substances—e.g., guarana, yerba mate, or kola nut—that further boost the caffeine load. These substances are often poorly studied and unregulated, and may interact with each other or with prescription drugs. However, caffeine appears to be the main active ingredient in the drinks. According to double-blind trials, the short-term effects of energy drinks seem to be as advertised: improved well-being and social extroversion, reduced depression and anxiety, and improved mood during fatiguing or cognitively demanding tasks. Manufacturers have rarely addressed the long-term effects of these drinks.

A systematic review identified 12 reported cases of emergence or exacerbation of symptoms in patients with bipolar disorder, Cluster B personality disorder, or schizophrenia in users of energy drinks. The majority of the cases were in patients with a history of mental illness; other patients had a family history of mental illness, and the only case with no prior susceptibility had very high levels of consumption, consistent with caffeine toxicity. These reports do not necessarily indicate that energy drinks are a problem when used in moderation by the general population, but rather that they may be problematic with excessive ingestion.

Also identified were 20 studies investigating the association of chronic energy drink consumption with stress, anxiety, and/or depression. Of these, 10 examined stress or stress-related outcomes. Results of 2 studies in patients with PTSD were mixed. Other studies did not measure stress directly as an outcome, had null results, or had mixed results depending on the outcome being measured. Most of the studies had cross-sectional designs, which preclude conclusions about causality.

The 8 studies of anxiety and 8 studies of depression had similarly conflicting results and cross-sectional designs. Only one of these studies reported a negative relationship between energy drinks and a symptom—in this case, anxiety. A considerable number reported positive relationships.

Since evidence of causality is lacking, an alternative explanation for these results may be that persons with low well-being, depression, or anxiety may self-medicate with the drinks for their acute positive effects. It is also possible that the association is mediated by dysregulated sleep.

Richards G, Smith A: A review of energy drinks and mental health, with a focus on stress, anxiety, and depression. *Journal of Caffeine Research* 2016;6 (June):49–63. From Cardiff University, U.K. **Source of funding not stated. The authors declared no competing interests.**

D-cycloserine Augmentation in OCD

Results of a large, well-designed clinical trial did not confirm the early promise of D-cycloserine augmentation of cognitive behavioral therapy (CBT) in pediatric obsessive-compulsive disorder.¹

Background: Results of pilot studies have suggested that D-cycloserine, an NMDA receptor partial agonist, may augment the effects of CBT, hypothetically by enhancing the extinction of learned fear during exposure exercises.^{2,3}

Methods: The present study enrolled 142 patients (aged 7–17 years) with OCD, who were either unmedicated or receiving stable doses of antidepressant or antipsychotic medication. Participants received 10 sessions of family-based CBT over 8 weeks using an abbreviated protocol. In addition, they were randomly assigned to receive weight-based D-cycloserine or placebo 1 hour before CBT sessions 4–10. The primary efficacy outcomes were change from baseline in the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total score and in the Clinical Global Impression (CGI)–Severity score.

Results: Both the D-cycloserine and placebo groups experienced significant improvement in obsessive-compulsive symptoms. The 2 treatment groups did not differ in the amount or timing of improvement; nor did they differ in any secondary outcome, including depressive and anxiety symptoms and parent-rated OCD impact. Response rates (CY-BOCS score ≤ 14) were about 60% at the last assessment (1 week after the end of treatment), and remission rates (CY-BOCS ≤ 12) were about 50%. In addition, 70–80% of participants were rated as "much improved" or better on the CGI–Improvement scale.

Previous research suggested that the effects of D-cycloserine might be blunted by treatment with an SRI antidepressant. However, the present study found no such interaction.

Discussion: Augmentation of CBT with D-cycloserine has had mixed results in pilot studies in adults and children with various anxiety disorders. Well-controlled clinical trials show no clear benefit, but post-hoc analyses of other studies suggest a possible role, according to an editorial.⁴ However, it is possible that any potential effect of D-cycloserine in the study might have been overshadowed by the strong efficacy of protocol-driven, family-based CBT. It is also possible that D-cycloserine might affect only fear-based symptoms (and not non-fear-based symptoms like ordering and symmetry), a hypothesis that the study was not designed to answer. It is also possible that D-cycloserine may enhance the effect of "good exposures" but could make "bad exposures" worse by consolidating fear memories.

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

¹Storch E, Wilhelm S, Sprich S, Henin A, et al: Efficacy of augmentation of cognitive behavior therapy with weight-adjusted D-cycloserine vs placebo in pediatric obsessive-compulsive disorder: a randomized clinical trial. *JAMA Psychiatry* 2016;73 (August):779–788. From the University of South Florida, Tampa; and other institutions. **Funded by the NIMH. Nine study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

²Storch E, et al: A preliminary study of D-cycloserine augmentation of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. *Biological Psychiatry* 2010;68(11):1073–1076. See *Child & Adolescent Psychiatry Alerts* 2010;12 (September):52.

³Farrell L, et al: Difficult-to-treat pediatric obsessive-compulsive disorder: feasibility and preliminary results of a randomized pilot trial of D-cycloserine-augmented behavior therapy. *Depression and Anxiety* 2013;30(8):723–731. See *Child & Adolescent Psychiatry Alerts* 2013;15(July):38–39.

⁴Hofmann S: Schrodinger's cat and D-cycloserine to augment exposure therapy—both are alive and dead [editorial]. *JAMA Psychiatry* 2016;73 (August):771–772.

*See Reference Guide.

Pharmacotherapy for Conduct Disorder

Evidence of the efficacy and safety of drugs to treat conduct disorder is limited, according to a systematic review. Although antipsychotics consistently demonstrate efficacy, they are associated with troubling adverse effects. Evidence for other drug categories is mixed.

Methods: The reviewers identified all randomized controlled trials published in English between 2000 and 2015 that were conducted in patients aged ≤ 18 years with a diagnosis of conduct disorder. To accurately represent conduct disorder, the criteria included studies of patients with comorbidities and those in whom conduct disorder was not the primary diagnosis. The included studies compared an active drug to placebo, 2 active pharmacotherapies, or multiple doses of a single drug. Outcomes of interest were efficacy, safety, and health-related quality of life (HRQoL).

Results: The search identified 12 clinical trials: 5 of divalproex, 3 of antipsychotics, 1 each of methylphenidate monotherapy, methylphenidate plus clonidine, atomoxetine, and lithium. A meta-analysis could not be conducted because of the heterogeneity of study designs and outcome measures. Patient ages ranged from 5 to 18 years, and comorbid diagnoses included ADHD, oppositional defiant disorder, PTSD, and disruptive behavior disorder NOS. Using standard criteria for systematic reviews, the evidence as a whole received a grade of "very low quality" because of a lack of uniform outcome measures, wide confidence intervals, and small sample sizes. Evidence of both safety and efficacy was of low quality. The management of treatment-related adverse effects was poorly documented. HRQoL was not frequently measured, but 2 drugs—atomoxetine and quetiapine—did have favorable effects.

Three studies investigated antipsychotics in children aged ≤ 12 years (risperidone and molindone) or adolescents (quetiapine). In a well-designed trial with a sample size of 118 patients, risperidone had positive effects in children with subaverage intelligence and severely disruptive behavior. The quetiapine study, with a sample size of only 19, found improvement in HRQoL and global severity of conduct disorder. Molindone improved behavior in patients with ADHD and conduct disorder and/or oppositional defiant disorder, but it is no longer available in the U.S.

One uncontrolled study found positive effects for clonidine, methylphenidate, or a combination of the 2 drugs. Methylphenidate was also effective in a second, monotherapy study. Dosing up to 40 mg/day may be required to improve symptoms including aggression and impulsivity.

Results were inconclusive in divalproex studies in patients with explosive temper and mood lability and in studies of adjunctive divalproex with stimulant treatment in children with ADHD and conduct problems. Lithium improved aggressive behavior in hospitalized children and adolescents but was associated with significant adverse effects. Atomoxetine also showed a high incidence of adverse effects, but produced positive effects on HRQoL in children with comorbid ADHD and conduct or disruptive behavior disorder.

Discussion: Psychosocial interventions are the best supported treatments for young patients with conduct disorder, but pharmacotherapy will often be used after other interventions have produced no, or limited, benefit. Despite the variety of medication options evaluated, this study revealed that evidence regarding their safety, efficacy, and impact on HRQoL is limited and additional research is needed.

Hambly J, Khan S, McDermott B, Bor W, et al: Pharmacotherapy of conduct disorder: challenges, options and future directions. *Journal of Psychopharmacology* 2016; doi 10.1177/0269881116658985. From Griffith University, Gold Coast, Australia; and other institutions. **Funded by Griffith University; and other sources. The authors declared no competing interests.**

Common Drug Trade Names: atomoxetine—*Strattera*; clonidine—*Catapres*; divalproex—*Depakene, Depakote*; methylphenidate—*Ritalin*; molindone (no longer available in U.S.)—*Moban*; quetiapine—*Seroquel*; risperidone—*Risperdal*

Parental Accommodation in Anxiety

In children and adolescents, parental accommodation—parents' modification of their behavior to reduce their child's distress—may contribute to the development and maintenance of anxiety disorders. According to results of a longitudinal study, parental accommodation of a child's anxiety may be a useful target for behavioral therapy of pediatric anxiety disorders.

Methods: Study participants were 62 patients, aged 6–17 years, who received treatment at a child and adolescent anxiety-disorders clinic. All participants participated in the 16-week Coping Cat program of cognitive behavioral therapy (CBT) for anxiety. Although the Coping Cat CBT program does not specifically address parental accommodation, some consideration of accommodation was likely introduced during psychoeducation or exposure tasks. Parental accommodation was measured with the 9-item Family Accommodation Scale-Anxiety and the 20-item Family Accommodation Checklist and Interference Score, which has subscales measuring the scope and burden related to accommodation. Child anxiety was assessed using the Multidimensional Anxiety Scale for Children, and response was defined as a Clinical Global Impressions–Improvement (CGI–I) rating of "much improved" or "very much improved."

Results: Parental accommodation was very common at baseline, with 86–98% of parents reporting ≥ 1 accommodating behavior. Following CBT, parents reported significant reductions in child anxiety (effect size, $d=1.08$). According to CGI–I criteria, 71% of the patients were treatment responders. Higher levels of pretreatment accommodation were significantly associated with higher symptom levels after treatment.

In addition to anxiety improvement, treatment was followed by significant reductions in parental accommodation (effect sizes, 0.69–0.88 depending on the measure used). Reductions in accommodation were positively associated with reductions in parent-rated child anxiety symptoms after therapy. However, changes in accommodation were not significantly associated with changes in clinician-rated anxiety severity.

Discussion: Results of this study are consistent with previous studies of parental accommodation in children with obsessive-compulsive disorder. It is unclear from this research whether reduced accommodation underlies improvements in children's anxiety or if reductions in the child's anxiety make parental accommodation unnecessary. Regardless, these results suggest it may be useful to address accommodation with parents of children with anxiety.

Kagan E, Peterman J, Carper M, Kendall P: Accommodation and treatment of anxious youth. *Depression and Anxiety* 2016; doi 10.1002/da.22520. From Temple University, Philadelphia, PA. **Source of funding not stated. One study author 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.

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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CHILD & ADOLESCENT PSYCHIATRY ALERTS

Agomelatine for ADHD.....	51
Brain Development Study Recruitment.....	49
Metformin for Antipsychotic Weight Gain	52
Pharmacotherapy for Opioid Use Disorders.....	49
Predicting Underage Drinking.....	50
Reference Guide	54
Sertraline-Associated EPS	53
Stimulants plus Guanfacine for ADHD.....	51

Volume XVIII / September 2016 / Number 9

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Adolescent Brain Development Study

The NIH has announced that recruitment for the Adolescent Brain Cognitive Development (ABCD) study—the largest long-term study of brain development and child health conducted in the U.S.—has begun and is expected to continue for the next 2 years. The study will follow the biological and behavioral development of >10,000 children, starting at ages 9–10 years and continuing through adolescence and into early adulthood. Advanced brain imaging, interviews, and behavioral testing will be utilized in an attempt to characterize how childhood experiences interact with each other and with the child’s biology to affect brain development and subsequent social and behavioral health. The ultimate goal of the study is to provide information that will help create future educational strategies, child-development innovations, research priorities, more effective public health interventions, and science-based policy decisions. The University of California, San Diego will be the ABCD coordinating center, and recruitment will be conducted through schools at 19 study sites across the U.S. A full list of recruiting sites, as well as additional information on the study, is available at www.ABCDStudy.org.

Recruitment begins for landmark study of adolescent brain development [press release]. Bethesda, Maryland: NIH; September 13, 2016.

Medication for Opioid Use Disorders

According to a policy statement from the American Academy of Pediatrics (AAP), medication-assisted treatment for opioid-addicted adolescents and young adults should be expanded.

Since 1991, the rate of "nonmedical use" of opioids—i.e., use without a prescription or more than prescribed—has more than doubled in adolescents and young adults. Rates of opioid use disorders have increased in parallel. These disorders tend not to remit without treatment. Currently 3 medications are indicated for treatment of severe opioid use disorder: methadone, naltrexone, and buprenorphine.

Methadone, an opioid agonist, is a well-established treatment, but federal regulations prohibit most methadone programs from admitting patients aged <18 years.

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Naltrexone, an opioid antagonist, has low potential for misuse or diversion. Although there is not yet strong evidence of its efficacy in adolescents, it seems a promising alternative, especially in those who have a coexisting alcohol-use disorder.

Buprenorphine is FDA approved for treating opioid addiction in patients aged ≥ 16 years. Like methadone, buprenorphine is an opioid agonist with less addiction potential than heroin or other opioids but still significant potential for misuse and diversion. Currently physicians are permitted to prescribe buprenorphine in general medical settings after completing an 8-hour training and obtaining a waiver. There is extensive evidence of the efficacy of buprenorphine in adults, but placebo-controlled studies of its efficacy in adolescent patients are lacking. In addition, patient access to buprenorphine is severely hampered by confusion, stigma, and limited resources. However, there is no evidence to date of safety concerns in younger patients.

The AAP advocates for increasing resources to improve access to medication-assisted treatment of opioid addiction, including both increasing resources for medication-assisted treatment and access to developmentally appropriate substance use disorder counseling.

AAP Committee on Substance Use and Prevention: Medication-assisted treatment of adolescents with opioid use disorders. *Pediatrics* 2016; doi 10.1542/peds.2016-1893. **Funded with internal AAP funds. The authors declared no competing interests.**

Common Drug Trade Names: buprenorphine—*Buprenex*; methadone—*Dolophine*; naltrexone—*ReVia*

Neural Predictors of Underage Drinking

A statistical model based on demographic, behavioral, neurocognitive, and neuroimaging data was able to predict adolescent initiation of moderate-to-heavy drinking with 74% accuracy.

Methods: Substance-naïve children and adolescents, aged 12–14 years, who were enrolled under strict criteria were followed in an effort to determine predictors of later heavy alcohol use. Adolescents were excluded if there was more than minimal experience with alcohol or drugs, prenatal alcohol exposure, premature birth, or any neurological or Axis I disorder. Each participant's data included demographic, socioeconomic, and developmental information, family history, and measures of psychopathology and mood. Participants ($n=137$) completed the Alcohol Expectancy Questionnaire, which assesses beliefs about the expected effects of drinking. Baseline neurocognitive tests assessed domains of cognitive function thought to be relevant to alcohol initiation. Participants also underwent anatomic and functional brain MRI, carried out under a visual working memory task that has been shown to predict future alcohol use. At follow-up, at approximately age 18 years, adolescents were classified as either continuous nonusers (drank at most moderately and on <12 lifetime occasions) or as moderate-to-heavy drinkers.

Results: At baseline, 97% of study participants had never used alcohol. By age 18 years, 51% were drinking at least moderately; of this group, three-fourths were heavy drinkers. Predictors of alcohol use included male gender, higher socioeconomic status, starting to date by age 14 years, conduct disorder-related behaviors, and positive expectations of the effects of alcohol. Neuropsychological predictors included poorer performance on executive-function tests and faster response on sustained attention tests, perhaps indicating impulsivity. Neuroimaging predictors included widespread cortical thinning and diminished blood-oxygen-level-dependent (BOLD) response contrast, which represent a more mature state-of-function that the authors termed "pseudomaturity". This condition has been observed in at-risk youth in other behavioral studies—e.g., in nicotine dependency—and may indicate a greater likelihood of sensation-seeking behavior.

Squeglia L, Ball T, Jacobus J, Brumback T, et al: Neural predictors of initiating alcohol use during adolescence. *American Journal of Psychiatry* 2016; doi 10.1176/appi.ajp.2016.15121587. From the Medical University of South Carolina, Charleston; and other institutions. **Funded by the National Institute on Alcohol Abuse and Alcoholism. The authors declared no competing interests.**

Agomelatine for ADHD

In a preliminary study, agomelatine had effects similar to those of methylphenidate in children with ADHD.

Background: Agomelatine is an investigational antidepressant approved for use in the European Union. Its combination of catecholaminergic and melatonergic effects suggests it could improve symptoms of ADHD, possibly by ameliorating circadian-rhythm disruptions that may modify disease severity.

Methods: The study enrolled 50 patients, aged 8–17 years, with a new diagnosis of ADHD, combined subtype (DSM-IV-TR). Patients were randomly assigned to 6 weeks of treatment with either 20 or 30 mg/day methylphenidate, depending on weight, or 15 or 25 mg/day agomelatine. The primary study outcome was change from baseline in the parent-rated ADHD Rating Scale-IV (ADHD-RS-IV).

Results: Both treatment groups showed significant improvement in ADHD symptoms by week 6 ($p < 0.001$ for both treatments). Parent-rated ADHD-RS-IV scores improved significantly by week 3. The 2 treatments did not differ with regard to effects on the total score or on either of the 2 subscales, Inattention and Hyperactivity/Impulsivity. (See table.) Teacher ratings on the ADHD-RS-IV, a secondary outcome, also showed large and similar improvements with both treatments. A total of 23 patients receiving agomelatine and 24 receiving methylphenidate were judged to be responders, with a $\geq 40\%$ improvement in the parent-rated ADHD-RS-IV score.

Adverse effects were similar in the 2 treatment groups, and all were mild to moderate and tolerable. Insomnia was reported in 6 children receiving methylphenidate and in 1 receiving agomelatine.

Discussion: Although agomelatine was effective in this study, this appears to be only the first study of the drug in children. The results require replication in larger samples and in patients with strictly inattentive or hyperactive subtypes of ADHD.

Salardini E, Zeinoddini A, Kohi A, Mohammadi-Reza M, et al: Agomelatine as a treatment for attention-deficit/hyperactivity disorder in children and adolescents: a double-blind, randomized clinical trial. *Journal of Child and Adolescent Psychopharmacology* 2016;26 (August):513–519. From Tehran University of Medical Sciences, Iran. **Funded by Tehran University. The authors declared no competing interests.**

Common Drug Trade Names: agomelatine (not available in the U.S.)—*Valdoxan*; methylphenidate—*Ritalin*

Parent-Rated ADHD-RS-IV Scores		
	Agomelatine (n=25)	Methylphenidate (n=25)
Total Score		
Baseline	33	34
3 Weeks	11.8	9.9
6 Weeks	9	8.2
Hyperactivity Subscale		
Baseline	17.7	17.5
3 Weeks	5.8	4.6
6 Weeks	4.6	3.9
Inattention Subscale		
Baseline	15.4	16.5
3 Weeks	5.9	5.3
6 Weeks	4.4	4.3

Combined Stimulants and Guanfacine in ADHD

In a randomized trial, the combination of guanfacine and extended-release dextmethylphenidate was modestly superior to each agent as monotherapy in children with ADHD. The results support the concept of targeting different neurotransmitter systems to achieve the recommended goal of remission.

Background: Experimental models indicate that combining treatments with optimal dopamine D₁ and α 2-adrenergic antagonism—i.e., dexamethylphenidate and guanfacine—might result in superior clinical and cognitive outcomes compared with monotherapy.

Methods: The study enrolled 207 patients, aged 7–14 years, with ADHD of any subtype and a Clinical Global Impression–Severity (CGI–S)* score of ≥ 4 . Patients were randomly assigned to receive either guanfacine or placebo for the first 4 weeks of the study, after which extended-release dexamethylphenidate or placebo was added. For the final 4 weeks, participants received flexible, but stable doses of 5–20 mg/day extended-release dexamethylphenidate plus placebo (n=69), 1–3 mg/day immediate-release guanfacine plus placebo (n=68), or both active drugs (n=70). Primary efficacy endpoints were the ADHD Rating Scale IV (ADHD-RS-IV) total score and Inattentive and Hyperactive-Impulsive subscales and the CGI–Improvement (CGI–I) score as assessed by blinded clinicians. Treatment response was defined as a CGI–I rating of "much improved" or "very much improved." A secondary response criterion—both CGI response and $\geq 30\%$ reduction from baseline in ADHD-RS-IV total score—was also assessed.

Results: All patients demonstrated significant improvements in ADHD symptoms over time, regardless of treatment group. In individual pairwise comparisons, combined therapy was significantly superior to guanfacine for both ADHD-RS-IV total score (p=0.04) and Inattentive score (p=0.02), but not for Hyperactive-Impulsive score. Improvements in all 3 scores were also numerically greater with combined treatment than with dexamethylphenidate, but none of these differences were statistically significant. Rates of CGI response were 81% for dexamethylphenidate, 69% for guanfacine, and 91% for the combination. Numbers needed to treat* for CGI response were 4.6 for the combination versus guanfacine and 10 for the combination versus dexamethylphenidate. According to the secondary response criterion, rates of response were 62% for dexamethylphenidate, 63% guanfacine, and 75% for the combination. Adverse events were mild to moderate in severity and occurred equally in the 3 groups. Combined treatment was not associated with adverse cardiovascular changes.

Discussion: These study results suggest a modest benefit of combining guanfacine and dexamethylphenidate over either agent as monotherapy. The authors point out that even modest improvements in efficacy may be worth pursuing if there is no increase in adverse events.

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

McCracken J, McGough J, Loo S, Levitt J, et al: Combined stimulant and guanfacine administration in attention-deficit/hyperactivity disorder: a controlled, comparative study. *Journal of the American Academy of Child and Adolescent Psychiatry* 2016;55 (August):657–666. From the University of California, Los Angeles. **Funded by the NIMH. Three study authors disclosed potentially relevant financial relationships; the remaining 8 authors declared no competing interests.**

Common Drug Trade Names: dexamethylphenidate, extended release—*Focalin XR*; guanfacine—*Intuniv, Tenex*

*See Reference Guide.

Metformin for Antipsychotic Weight Gain in Autism

In a randomized clinical trial, metformin was effective in decreasing antipsychotic-induced weight gain in children and adolescents with autism spectrum disorder (ASD).¹

Background: Both risperidone and aripiprazole improve irritability and agitation in young patients with ASD. However, both can cause significant weight gain, and greater cumulative exposure has been associated with diabetes risk. The present study was undertaken to evaluate the weight-loss effects of metformin in children with ASD who were receiving an atypical antipsychotic. The authors took into account the concern that gastrointestinal (GI) adverse effects of metformin could overlap with existing GI symptoms common in ASD, potentially increasing irritability in children who cannot readily communicate discomfort.

Methods: Study subjects were 60 young patients, aged 6–17 years, with a diagnosis of ASD who had been receiving stable atypical antipsychotic medication for ≥ 1 month. Participants had gained $>7\%$ in body mass index (BMI) since starting the antipsychotic, or had a $>5\%$ increase per year in weight starting from a BMI ≥ 85 th percentile. Participants received 16 weeks of randomized, double-blind metformin or placebo. Metformin was provided as a liquid suspension, titrated to a maximum dosage of 500 mg b.i.d. in children aged 6–9 years and to a maximum of 850 mg b.i.d. in older patients. The primary outcome measure was change from baseline in the BMI z score,* which is an adjustment of the BMI for age and gender.

Results: Nearly all study patients were taking risperidone or aripiprazole at baseline; a total of 4 patients were treated with olanzapine or ziprasidone. In addition, nearly all of the patients were obese according to standard BMI criteria. The mean final daily dose of metformin was 1000 mg in 6–9 year olds and nearly 1600 mg in older patients.

After 16 weeks, metformin was associated with a significant decrease from baseline in the BMI z score, while scores remained stable in the placebo group ($p=0.003$; effect size,* 0.82). Weight remained stable in the metformin group and increased by about 6 lbs in the placebo group. A decline in BMI of $\geq 5\%$ occurred in 3 patients in the metformin group (11%). Benefits of metformin treatment were not evident until after 8 weeks. No significant change in metabolic variables was observed in either group.

Adverse effects of metformin and placebo were similar, but patients taking metformin experienced more GI adverse effects. Because metformin can cause GI upset, there was concern that weight control may have been a consequence of GI disturbance. However, patients who had GI symptoms experienced somewhat greater increases in BMI and weight than those without discomfort.

Editorial.² The authors of this study have provided a compelling solution for antipsychotic-induced weight gain in young people with autism. Other treatments have been investigated for antipsychotic-induced weight gain, including topiramate, which can cause important adverse effects, and stimulants and nutritional counseling, which have not been effective. Because most parents would prefer a single medication rather than a second drug to control adverse effects of the first, ziprasidone—the only atypical antipsychotic not associated with weight gain—may also warrant investigation for this indication.

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

¹Anagnostou E, Aman M, Handen B, Sanders K, et al: Metformin for treatment of overweight induced by atypical antipsychotic medication in young people with autism spectrum disorder: a randomized clinical trial. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.1232. From Holland Bloorview Kids Rehabilitation Hospital, Canada; and other institutions. **Funded by the US Department of Health and Human Services. Eleven study authors declared financial relationships with commercial sources; the remaining 14 authors declared no competing interests.**

²McDougle C: Atypical antipsychotic-induced weight gain in children and adolescents: sometimes less is more [editorial]. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.1213. From Massachusetts General Hospital, Lexington, MA. **The author declared no competing interests.**

Common Drug Trade Names: aripiprazole—*Abilify*; metformin liquid—*Riomet*; olanzapine—*Zyprexa*; risperidone—*Risperdal*; topiramate—*Topamax*; ziprasidone—*Geodon*

*See Reference Guide.

Sertraline-Associated EPS

A 16-year-old boy was admitted with a history of worsening depression and onset of suicidal thoughts. He had no personal or family history of any psychotic disorder. He was started on 500 mg/day valproate to stabilize mood, and 50 mg/day sertraline, titrated to 200 mg/day, for major depression. He experienced mild gastrointestinal symptoms when the sertraline dosage reached 200 mg/day but no other immediate adverse effects. Three weeks after

starting sertraline, the patient became restless and irritated and exhibited disturbed behavior. Alprazolam was administered, and the sertraline dosage was reduced; however, the symptoms did not improve. The following day, the abnormal behaviors escalated and he experienced uncontrollable finger curling, neck extension, and excessive rigidity in his arm muscles. Symptoms did not resolve with diazepam administration. Serum creatine phosphokinase was found to be elevated, and sertraline was stopped. On the next day, the patient's mood stabilized but he continued to experience facial spasms, tight arms, and curled fingers, and he was unable to remain still. Intramuscular scopolamine hydrobromide was administered for several days, and all movement symptoms resolved. Valproate had been continued unchanged throughout the episode. Citalopram was started, and after stabilization, the patient was discharged and continued to improve with no further movement symptoms.

Among the SSRIs, sertraline is considered relatively safe for adolescent use, but extrapyramidal symptoms (EPS) have been reported in adults. It is unlikely that concomitant use of valproate contributed to the EPS in this patient, as it was unchanged during the episode, but causality could not be firmly established for sertraline. Regardless, this case highlights the need to be aware of the possibility of EPS with adolescent SSRI use.

Wang L-F, Huang J-W, Shan S-Y, Ding J-H, et al: Possible sertraline-induced extrapyramidal adverse effects in an adolescent. *Neuropsychiatric Disease and Treatment* 2016;12:1127–1129. From Zhejiang University School of Medicine, China; and other institutions. **Funded by the National Clinical Research Center for Mental Health Disorders. The authors declared no competing interests.**

Common Drug Trade Names: alprazolam—*Xanax*; citalopram—*Celexa*; diazepam—*Valium*; sertraline—*Zoloft* valproate—*Depakote*

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.

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 score of 0 means the score is the same as the mean.

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CHILD & ADOLESCENT PSYCHIATRY ALERTS

Brain Stimulation for Depression	56
Cognitive Psychological Treatment for Tics	58
Parental Depression: Impact on Offspring	57
Reference Guide	60
Stimulants and Bone Mass	55
Suicide in Children and Adolescents.....	59

Volume XVIII / October 2016 / Number 10

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Stimulants and Bone Mass

Use of stimulants was associated with reduced bone mineral content (BMC) and bone mineral density (BMD) in children and adolescents. Because adolescence and young adulthood are crucial years for bone mass accrual, stimulant use may increase risk of osteoporosis later in life.

Methods: A cross-sectional analysis was conducted using data from the U.S. National Health and Nutrition Examination Survey collected between 2005 and 2010. All participants who were aged 8–20 years and who underwent dual-energy x-ray absorptiometry scans were included in the analysis. Medication use was ascertained using a questionnaire administered by an interviewer either to the participant (if >16 years) or to a parent (for younger study subjects). The analysis was adjusted for age, gender, race/ethnicity, socioeconomic status, physical activity, and z scores for height, weight, and body mass index (BMI).

Results: Of 6489 study participants, 159 reported stimulant use. Stimulants were associated with significantly lower BMIs and weight in both male and female participants, but they were within the clinically acceptable reference range. Stimulant users were also significantly shorter than non-users. All analyses were adjusted for these differences. Physical activity and socioeconomic status did not differ between stimulant users and nonusers.

Stimulant use was associated with lower bone mass at all sites measured: lumbar spine, total femur, and femoral neck. Specifically, stimulant users had significantly lower lumbar spine BMC ($p=0.02$) and BMD ($p=0.03$) and femoral neck BMC ($p=0.03$). Values for femoral neck BMD and total femur BMC and BMD were lower but did not reach statistical significance.

Participants reported receiving stimulants for a mean of about 3 years. Three months of therapy was chosen as the minimal treatment duration to observe an effect on bone physiology. Effects were not observed in the 24 participants who received stimulants for <3 months, but all measures of bone density were reduced in the 135 participants with longer exposure.

Discussion: Amphetamines increase concentrations of postsynaptic norepinephrine, which suppresses bone formation and stimulates bone resorption. There have been few studies of

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stimulants' effects on bone in adults, and almost none in children and adolescents. Skeletal status during childhood is a strong predictor of peak bone mass in young adulthood. Changes in BMD on the order of those observed in the present study could increase the risk of future fractures.

Feuer A, Thai A, Demmer R, Vogiatzi M: Association of stimulant medication use with bone mass in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA Pediatrics* 2016; doi 10.1001/jamapediatrics.2016.2804. From Weill Cornell Medicine, New York, NY; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

Brain Stimulation for Adolescent Depression

MRI-guided, high-frequency, repetitive transcranial magnetic stimulation (rTMS) was effective and well tolerated in adolescents with treatment-resistant depression in a small, uncontrolled study.

Methods: Study subjects were 10 adolescents (mean age, 16 years) who were experiencing depression despite ongoing treatment with an SSRI or SNRI. Participants were also required to have experienced nonresponse to ≥ 1 prior medication trial. MRI was used to estimate the location of the left dorsolateral prefrontal cortex in a 5-minute procedure, and a scalp target was identified for coil placement. Patients received rTMS 5 days per week for 6–8 weeks, for a total of 30 sessions. Clinical outcomes included change from baseline in the Children's Depression Rating Scale-Revised (CDRS-R), the Quick Inventory for Depressive Symptomatology Adolescent 17-Item Self-Report (QIDS-A17-SR), and the Clinical Global Impression–Severity (CGI-S)* and Improvement (CGI-I)* scales. These scores were measured at baseline, after 10, 20, and 30 treatments, and at 6-month follow-up. Baseline antidepressant medications were continued throughout the study.

Results: The 10 enrolled adolescents had been experiencing depression for an average of nearly 2 years and had an average of 4 previous medication trials. Baseline scores on the symptom scales indicated severe depression.

Of the 7 participants who completed treatment, 6 were considered responders. Of those who did not complete treatment, 1 withdrew after the first rTMS session because of scalp discomfort, 1 was hospitalized after 5 sessions for worsening depression, and 1 withdrew after 17 sessions because of anxiety about school expectations, although her clinicians and parents felt her depression was improving.

Change from baseline in depression was calculated using all 10 participants. Changes in the CDRS-R were statistically significant beginning at treatment 10, and scores continued to improve through the end of treatment and beyond. (See table.) Improvement in QIDS-A17-SR became significant after treatment 20, and CGI-S ratings at treatment 10. At the end of treatment, 6 of 10 participants were rated as mildly ill, borderline ill, or normal. CGI-I ratings were "much improved" or "very much improved" at 6-month follow-up in 6 patients.

Change from Baseline in Depression			
	Mean Baseline Score	Mean End of Treatment Score	Mean 6-Month Follow-Up Score
CDRS-R	63	42; p=0.002	40; p=0.03
QIDS-A17-SR	16	12; p=0.045	10; p=0.03
CGI-S	5.4	3.4; p=0.002	3.0; p=0.002

Neurocognitive testing did not suggest any decline in functioning during treatment. A total of 8 patients reported suicidal thinking during the week prior to starting treatment. Suicidal behavior worsened during the trial in 2 patients: 1 due to life circumstances, and 1 who had self-injurious behavior during follow-up.

Discussion: The optimal technique for rTMS treatment of depression is controversial, and there has been particularly little research in adolescents. In addition to evaluating efficacy, this study examined 3 localization techniques for coil placement: the MRI-guided placement used for actual stimulation, the "5-cm rule" method (5 cm anterior of a location visually identified during motor stimulation) and the "Beam F3" method (a computer-generated calculation based on 3 anthropometric scalp measurements). Although comparison of the targeting methods for coil placement showed statistically significant differences among the 3 methods, the clinical implications of this finding are unclear, and MRI-guided techniques are not likely to be widely used in adolescents because they could be a barrier to treatment.

Wall C, Croarkin P, Maroney-Smith M, Haugen L, et al: Magnetic resonance imaging-guided, open-label, high-frequency repetitive transcranial magnetic stimulation for adolescents with major depressive disorder. *Journal of Child and Adolescent Psychopharmacology* 2016;26 (September):582–589. From PrairieCare Medical Group, Rochester, MN; and other institutions. **Funded by the Klingenstein Third Generation Foundation; and other sources. Four study authors disclosed financial relationship with commercial sources; the remaining 4 authors declared no competing interests.**

*See Reference Guide.

Lifetime Impacts of Parental Depression

Offspring of parents with depression are at increased risk of depression, medical illness, and mortality into middle age, according to results of a 30-year follow-up study.¹ Because depression is common and most frequently affects women of childbearing age, the impact of maternal depression is an important public health concern.²

Methods: A clinical cohort of adults with moderate-to-severe major depressive disorder and a community sample of controls with no lifetime history of psychiatric illness were recruited for the study in 1982. Across 6 study waves spanning >33 years, both parents in each family and their biological offspring were interviewed using adult and child versions of the Schedule for Affective Disorders and Schizophrenia and the Global Assessment Scale. Data on medical illness were collected using a standardized checklist.

Results: At the 30-year follow-up, data were available for 159 offspring (about 60% of those enrolled), who had been first assessed at an average age of 19 years and were followed for a mean of 28 years. The offspring of parents with depression had 2-fold increases in mood disorders and in anxiety disorders, largely due to increased rates of depression and phobias. (See table.) Specific phobias accounted for the large majority of phobias in both high-risk offspring and controls. Offspring of parents with depression also had higher rates of drug dependence, although this difference fell short of statistical significance. Relative risks* of mood disorder were similar regardless of depression severity in parents.

Cumulative Incidence of Psychiatric Disorders in Offspring				
Diagnosis in Offspring	Parents with Depression (n=103)	Parents Without Depression (n=44)	Relative Risk	Significance
Any Mood Disorder	85%	61%	2.02	p=0.004
Major Depressive Disorder	74%	34%	3.18	p<0.0001
Any Anxiety Disorder	72%	48%	2.02	p=0.004
Specific Phobia	52%	27%	2.47	p=0.02

Regardless of parental depression, the peak incidence of anxiety disorders was before puberty and in early adolescence, and peak depression onset was in late adolescence. Offspring of parents with depression had a 10-fold higher relative risk of prepubertal-onset major depression. Their incidence of new-onset depression remained elevated in adolescence and through the 20–40 year age span, returning to control levels only after the age of 40 years.

At the 20-year follow-up, the high-risk group also had a significantly increased incidence of medical illnesses, particularly cardiovascular and neuromuscular disorders. The difference narrowed at the 30-year point, probably due to the aging of the low-risk group. There were no deaths from unnatural causes in the low-risk group but 5 in the high-risk group, including 2 suicides and 2 overdoses. One of these deaths occurred in an adolescent, and 4 in individuals in their 30s or 40s.

Discussion: Other studies have suggested lasting adverse effects of parental depression, but this is the first to cover the full age of risk for major depressive disorder.

¹Weissman M, Wickramaratne P, Gamberoff M, Warner V, et al: Offspring of depressed parents: 30 years later. *American Journal of Psychiatry* 2016;173 (October):1024–1032. From Columbia University, New York, NY; and other institutions. **Funded by the NIMH; and other sources. Two study authors disclosed financial relationships with commercial sources; the remaining 7 authors declared no competing interests.**

²Hammen C: Children of depressed parents: the long view [editorial]. *American Journal of Psychiatry* 2016;173 (October):956–957. From the University of California, Los Angeles. **The author declared no competing interests.**

*See Reference Guide.

Cognitive Psychophysiological Treatment for Tics

A therapy focusing on the processes underlying tics, first developed for adults and then manualized for children, reduced tics in a consecutive case series of 7 young patients. The treatment also had mixed but generally positive effects on adaptive aspects of behavior.

Background: The cognitive psychophysiological (CoPs) treatment for tics in adults focuses on processes influencing thoughts and behaviors underlying tics, rather than on the tics themselves. The treatment targets cognitive factors such as anticipation, rigid beliefs, and perfectionistic planning and also deals with the physiological tension buildup that precedes tic onset.

Methods: Study participants, aged 8–12 years, had been consecutively referred to a tic clinic and received a modification of CoPs treatment called Facotik. Each child, with a parent, participated in 12–14 weekly 90-minute therapy sessions, interspersed with homework. The content of the program consisted of awareness training; muscle discrimination; relaxation; reducing sensorimotor activation; modifying the style of planning action; cognitive restructuring of anticipation and appraisals; behavioral restructuring; global restructuring; generalization; and relapse prevention. Effects of treatment were measured with the Yale Global Tic Severity Scale (YGTSS); the Tourette's Syndrome Global Scale (TSGS); the Behavior Assessment System for Children, Second Edition (BASC-2); and the Culture Free Self-Esteem Inventory.

Results: Of 13 children enrolled in the study, 6 did not complete treatment and follow-up evaluation, including 4 who withdrew during therapy. Results were reported for the 7 children (mean age, 10 years; 6 boys) who completed treatment and follow-up.

After treatment, parents reported a significant decrease in their child's tics on the YGTSS. Children did not perceive a decrease in tics on average, although 4 individual children did. On the 2 subscales of the YGTSS, parents reported significant decreases in severity and impairment, while children only reported a decrease in severity. Both parents and children observed significant improvement on the TSGS global scale, with improvement in tics but not in social functioning. There were no globally significant improvements in adaptive behavior on the

BASC-2, and clinical improvement on individual aspects of behavior was variable. One child showed improvement in self-esteem, and the others already had medium-to-high levels of self-esteem before treatment. All reported that the self-monitoring diary and relaxation exercises were most helpful.

Discussion: The discrepancy between parent- and child-reported improvement in tics may have arisen from the treatment's heightening of children's awareness of their tics. The lack of improvement in impairment may be attributable to comorbid symptoms. Longer follow-up of the study participants, a randomized clinical trial, and publication of the Facotik manual are planned.

Leclerc J, O'Connor K, J-Nolin G, Valois P, et al: The effect of a new therapy for children with tics targeting underlying cognitive, behavioral, and physiological processes. *Frontiers in Psychiatry* 2016; doi 10.3389/fpsy.2016.00135. From the Centre de recherche de l'Institut universitaire en sante mentale de Montreal, Canada; and other institutions. **Funded by the Fonds de la Recherche en Sante du Quebec.** All study authors declared financial relationships with commercial sources.

Child, Early Adolescent Suicides Differ

According to an analysis of multistate suicide data, children who commit suicide are more likely than young adolescents to have impulsivity problems and less likely to be experiencing depression.

Methods: The National Violent Death Reporting System (NVDRS) is a state-based surveillance project that collects data from death certificates and other sources. The present analysis included NVDRS data on suicide deaths in persons aged 5–14 years, drawn from 17 states from 2003 to 2012. Suicide is defined by the NVDRS as a death resulting from the use of force against oneself, which evidence indicates was intentional. Comparisons were made between children (aged 5–11 years) and early adolescents (aged 12–14 years). To explore recent reports of increasing rates of suicide in elementary school-aged black children, comparisons were also made between black and non-black racial subgroups.

Results: The analysis included 87 suicides in children and 606 in early adolescents. Compared with early adolescents, children who died by suicide were more likely to be male or black, to have died by hanging, strangulation, or suffocation, and to have died without leaving a suicide note. (See table.) They were also more likely to have died at home and to have experienced relationship problems with family members and friends. Young adolescents were more likely to be experiencing depression and to have boyfriend/girlfriend problems. An identical proportion of both age groups (29%) disclosed their suicidal intent to another person before death.

Differences in individual characteristics and precipitating circumstances between child and adolescent suicides			
	Children (n=87)	Young Adolescents (n=606)	Significance
Percent male	85%	70%	p=0.003
Percent black	37%	12%	p<0.001
Method			
Firearm	14%	30%	p=0.008
Hanging/strangulation/suffoca-	81%	64%	
Suicide note present	8%	30%	p<0.001
Current depressed mood	17%	31%	p=0.009
Mental health diagnosis[†]			
Depression/dysthymia	33% (9/27)	66% (120/183)	p=0.001
ADHD	59% (16/27)	29% (53/183)	p=0.002

[†]Proportion of all with a mental health problem

A current mental health problem was observed in about one-third of those who committed suicide. Age groups did not differ in the prevalence of a mental health problem or in rates of mental health treatment. Among those with an observed mental health problem, ADHD was more common in children and depression was more common in adolescents. (See table, previous page.)

Rates of alcohol and substance abuse were low in the entire group and did not differ according to age. About 4% of children and 8% of adolescents tested positive for opiates, higher rates than for alcohol or other illicit drugs.

Discussion: Although suicide is rare in this age group, it ranked 10th as a cause of death in elementary school-aged children in 2014. The high rate of ADHD in child suicides indicates that these children may have been more vulnerable as a group to respond impulsively to interpersonal difficulties. This observation suggests traditional suicide-prevention strategies, which are focused primarily on depression, may be off target. Although other research suggests black children are less likely than white children to receive services for mental or emotional problems, the present data suggest the circumstances surrounding suicide are similar regardless of race.

Sheftall A, Asti L, Horowitz L, Felts A, et al: Suicide in elementary school-aged children and early adolescents. *Pediatrics* 2016; doi: 10.1542/peds.2016-0436. From Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus; and other institutions. **Funded by the NIMH; and the CDC. The 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.

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CHILD & ADOLESCENT PSYCHIATRY ALERTS

Digital Parent Training	62
Mindfulness-Based Interventions.....	61
Paternal Substance Abuse.....	65
Psychological Depression Prevention.....	63
Reference Guide	66
Stimulants and Adaptive Function.....	64

Volume XVIII / November 2016 / Number 11

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Review of Mindfulness-Based Interventions in Adolescents

Mindfulness instruction is believed to facilitate self-regulation and coping, particularly during stressful experiences. The goal of mindfulness-based practices is to help with acceptance, but many mindfulness programs balance this acceptance with behavioral change. Mindfulness-based stress reduction (MBSR) was first developed to help adults cope with chronic pain and ongoing stressors. Newer mindfulness-based interventions include mindfulness-based cognitive therapy (MBCT), dialectical behavior therapy, acceptance and commitment therapy, and mindfulness-based relapse prevention. These approaches have multiple clinical applications in adults, including prevention and treatment of depression, generalized anxiety disorder, suicidal behavior, and bipolar disorder. The research base for mindfulness training in children and adolescents is much smaller than in adults.

Existing mindfulness-based interventions have been adapted for young people by using shorter meditation practice periods, developmentally appropriate language, and age-appropriate mindfulness activities. There have been encouraging preliminary reports on the acceptability, feasibility, and clinical benefit of mindfulness training. Positive effects of MBSR in various samples of at-risk adolescents include improved relationships, coping, and self-regulation as well as reduced stress, anxiety, rumination, and conflict engagement. In a large randomized controlled trial (n=300), a school-based MBSR program was associated with reduced depressive symptoms, negative coping, negative affect, somatization, self-hostility, and posttraumatic stress symptoms, compared with an active control intervention. Other clinical trials have shown benefit for MBSR in adolescents in outpatient psychiatric treatment and as a complementary intervention for substance abuse.

Fewer studies have evaluated MBCT in adolescents. These programs have also been adapted for younger patients by having shorter sessions, smaller groups, limit-setting to prevent misbehavior, incentives for attendance and homework, and family involvement. MBCT has been evaluated mainly in small, uncontrolled studies. In pre- and early adolescents, MBCT reduced

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internalizing symptoms and improved attention problems. Studies in adolescents have addressed externalizing behavior problems, ADHD, and depression.

Mindfulness techniques have the potential to change adolescents' relationship with stressors in a positive way, potentially reducing risk of depression, anxiety, and risk-taking behavior. These techniques may be beneficial for youth presenting with behavioral, emotional, and somatic symptoms. However, there remains a need for rigorous scientific evaluation of mindfulness-based interventions for adolescents in well-designed controlled trials.

Perry-Parrish C, Copeland-Linder N, Webb L, Shields A, et al: Improving self-regulation in adolescents: current evidence for the role of mindfulness-based cognitive therapy. *Adolescent Health, Medicine and Therapeutics* 2016;7: 101–108. From Johns Hopkins School of Medicine, Baltimore, MD. **Source of funding not stated. The authors declared no competing interests.**

Digital Parent Training for Disruptive Behavior

According to results of a meta-analysis, digital parent training is an effective and potentially scalable intervention for children with disruptive behaviors. Effects are modest overall but more pronounced in young children with behaviors in the clinical range.

Methods: A comprehensive literature search identified controlled trials of parent training interventions targeting disruptive behavior problems that were measured using a valid scale. For inclusion, interventions had to be delivered by digital media designed primarily to replace human support; they were not to be used in tandem with therapy. In addition, studies were required to report ≥ 1 of 3 outcomes—child behavior, parent behavior, or parental confidence in self-efficacy—and to have 1 active intervention group and a control group with ≥ 5 participants in each group.

Examples of Digital Training Program Studied		
Intervention	Format	Focus
Parenting Wisely	Self-administered software program with scenario-based learning design and a supplementary workbook	To modify parent–child interactions that reinforce antisocial behavior, using refraining and cognitive restructuring
Comet	7 online interactive sessions distributed over 10 weeks plus homework	Targets parents' reactions and activities to promote behavioral change in the parent and then the child
Based on Triple P Program	7 online downloadable podcasts, ranging from 9 to 14 minutes each, discussing parenting skills revolving around disruptive behaviors (e.g., dealing with aggression, sharing) delivered in a conversational format	Promotes nurturing parenting behaviors, a low conflict environment, and children's social and emotional well-being through positive parenting practices
Based on 1-2-3 Magic Parenting Program	2 digital videos viewed over 2 weeks, which include lecture components explaining the parenting strategies and their application at home and in public, as well as numerous role-played video vignettes, demonstrating maladaptive parent–child interactions, and the more adaptive parenting techniques	Teaching parents techniques of established behavioral, emotional, and cognitive principles, and providing guidance on ways to reduce children's disruptive behaviors

Results: The analysis included 7 studies with a total of 718 participants—329 receiving the intervention and 389 controls. In all studies, the control group was placed on a waiting list and received no treatment. Four of the 7 studies were conducted in younger children (average age, 4–7 years), and 3 were conducted in middle school-aged children (average age, 12–14 years). All 4 studies in younger children targeted behavior in the clinical range, and all 3 in older children targeted less severe disruptive behavior. Interventions were delivered online, by DVD or CD-ROM, via podcast, or on computers at community centers. All of the interventions were based on theoretically driven, evidence-based content targeting parents' beliefs and behaviors regarding child-rearing and discipline. The studies were generally of high methodological quality, and there was no evidence of publication bias.

Digital parent training resulted in significantly greater improvement than the control condition in all 3 outcomes. Effect sizes* for specific outcomes were 0.44 for improvement in child behavior, 0.41 for improvement in parent behavior, and 0.36 for parent confidence in self-efficacy. Improvements were larger in the studies of young children with clinically significant disruptive behavior, and in these younger children, interactive programs had larger effects than noninteractive ones (effect size for interactive programs vs. control in younger children, 0.82). Improvements were sustained during follow-up of up to 6 months.

Discussion: Behavioral parent training is considered the first-choice treatment for disruptive behavior disorders but is underutilized, leading to poor quality of care and potential overuse of medications. Parent training programs are among the oldest and best studied technology-based interventions. Future studies should compare digital with therapist-led programs and evaluate the role of digital programs as a pathway to engaging families with more formal services.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis, but the source of funding was not included.

Baumel A, Pawar A, Kane J, Correll C: Digital parent training for children with disruptive behaviors: systematic review and meta-analysis of randomized trials. *Journal of Child and Adolescent Psychopharmacology* 2016;26 (October):740–749. From Zucker Hillside Hospital, Glen Oaks, NY; and Hofstra North Shore LIJ School of Medicine, Hempstead, NY. **Source of funding not stated. Two study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

*See Reference Guide.

Psychological Interventions to Prevent Depression

Evidence-based psychological treatments are only modestly effective at preventing the onset of depressive disorder in children and adolescents, according to a Cochrane review.

Background: Cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) have been the basis of most depression-prevention programs. Both types of intervention have robust supporting evidence for the treatment of depression and therefore seem to be a "good best bet" for prevention. The present, updated Cochrane review evaluates these as well as third-wave CBT, which includes acceptance and commitment therapy and dialectical behavioral therapy, among others.

Methods: Included in the review were all available randomized controlled trials of evidence-based psychotherapeutic interventions for depression prevention conducted in populations with an average age of 5–19 years. Target groups could include general populations, persons with risk factors for depressive disorder, and those with an elevated but subclinical level of depressive symptoms. Onset of major depressive disorder in the 4–12 months after baseline and the level of depressive symptoms on a standardized self-report questionnaire were the primary outcomes.

Results: A total of 83 trials met inclusion criteria: 29 conducted in unselected populations and 53 in targeted populations. The vast majority of programs (n=67) were offered in schools, 8 were offered in colleges or universities, 4 in clinical settings, and the rest in mixed settings. The overall quality of the studies was rated as low-to-moderate.

Depression onset within 12 months was evaluated in 32 trials with nearly 6000 subjects. In these studies, risk for receiving a diagnosis of depression was reduced with active treatment. Although the reduction was statistically significant ($p=0.01$), the absolute difference between groups who did and did not receive an intervention was small (risk difference, -0.03).

Levels of depressive symptoms were evaluated in 70 of the trials, with nearly 14,000 participants. Again the results were statistically significant in favor of the intervention ($p<0.0001$), but small with a standardized mean difference* in symptoms of 21% at the post-treatment. Significant but modest differences in symptoms from placebo were observed at 3–12 months, but no differences were evident after 12 months.

Programs carried out in unselected populations were less effective than those conducted in targeted populations. However, studies of targeted populations were limited by the lack of comparison to an attention placebo—i.e., a placebo that provides some amount of attention but is nonspecific, such as psychoeducation. Overall, the number needed to treat* to prevent 1 depression diagnosis was 33.

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

Hetrick S, Cox G, Witt K, Bir J, et al: Cognitive behavioural therapy (CBT), third-wave CBT and interpersonal therapy (IPT) based interventions for preventing depression in children and adolescents (review). *Cochrane Database of Systematic Reviews* 2016; doi 10.1002/14651858.CD003380.pub4. From Orygen, the National Centre of Excellence in Youth Mental Health, Melbourne, Australia; and other institutions. **Funded by the University of Auckland; and the Health Research Council, New Zealand. The authors disclosed no financial relationships with commercial sources.**

*See Reference Guide.

Stimulants and Adaptive Functioning in ADHD

In a small cohort of children, stimulant treatment was associated with improvement in adaptive skills, an area of substantial dysfunction in many patients with ADHD.

Background: Adaptive functioning refers to the performance of daily activities required for personal and social sufficiency. It is defined by performance, not ability. Children with ADHD often have significant deficits in this area, but there have been few studies of adaptive functioning as an outcome measure of pharmacological treatment of ADHD.

Methods: Study participants were 27 children, aged 6–16 years, referred for initial evaluation and treatment of ADHD. The Adaptive Behavior Assessment System–Second Edition (ABAS-II)—a validated questionnaire that assesses 3 domains of adaptive skills: conceptual, social, and practical—was administered by teachers. Following the assessment, all children received treatment with stimulants, predominantly methylphenidate (*Ritalin*), and a follow-up evaluation was conducted 4–5 years later. Teachers again administered the ABAS-II, and an increase in score of $\geq 15\%$ from baseline was considered clinical improvement.

Results: Of the original 27 children, 9 had reached age 18 years and were no longer available for follow-up, 5 had stopped treatment and were no longer in contact with the clinic, and 1 declined participation. The remaining 12 children (7 boys) who underwent the second evaluation had a mean age of 15 years (range, 13–17 years). Participants showed a significant mean increase of about 20–25 points in ABAS-II total scores ($p=0.019$) as well as the

conceptual and practical domains ($p=0.019$ and $p=0.014$, respectively). Improvement was also evident in the social domain, but the change did not reach statistical significance ($p=0.062$). Although there were considerable variations among the children, the majority improved to average adaptive levels from levels far below average. All 5 girls demonstrated a $\geq 15\%$ increase in their total ABAS-II scores, compared with 3 of the 7 boys. Adaptive behavior worsened in 1 boy and remained essentially unchanged in 3.

Discussion: This study had several important limitations including the small sample size, the nonrandomized design, and the lack of a comparison group. Moreover, the study group consisted of a patients specifically selected because they had chosen to continue pharmacological treatment. In addition, a regression to the mean effect cannot be ruled out. However, the results suggest that adaptive functioning may be improved with stimulant treatment. The results also indicate that an instrument like the ABAS-II could be a valuable additional tool that could facilitate collaboration between schools and clinics. The finding of greater improvement in girls may have been a chance occurrence and should be studied further.

Lindblad I, Nasic S, Landgren M, Svensson L, et al: Adaptive skills are useful for evaluating the effect of pharmacological treatment of children with attention-deficit/hyperactivity disorder. *Acta Paediatrica* 2016; doi 10.1111/apa.13631. From the University of Gothenburg, Sweden; and other institutions. **This study was conducted without funding. The authors declared no competing interests.**

Paternal Substance Use Disorders

Increased impulsivity in children with a family history of substance use disorders may make them less able to regulate sensation seeking drives that peak in adolescence, which may increase risk for developing substance use disorders.

Methods: Study participants were enrolled as preadolescents (aged 10–12 years) and included 305 children with biological fathers who had drug or alcohol problems and 81 children with no family history of substance problems. Children who were using substances at baseline were excluded. Children and their parents were assessed at baseline, and the children underwent drug and alcohol screens at 6-month intervals for a median of 30 months. Impulsiveness was measured with the Barratt Impulsiveness Scale (BIS-11), and sensation seeking with the Sensation Seeking Scale for Children. Family-history-positive preadolescents who began using drugs or alcohol during follow-up ($n=58$; before age 15 years) were propensity score matched* with a control group of those who did not initiate substance use before age 15 years.

Results: At baseline, preadolescents with a positive family history had significantly higher BIS-11 scores for overall impulsiveness ($p<0.05$) and for 2 of the measure's 3 subscales—non-planning impulsiveness and attentional impulsiveness (i.e. spontaneity and distractibility, respectively; $p<0.05$ for both). Across early adolescence, the trajectory of all of the impulsiveness measures did not differ between the family-history-positive and negative cohorts. The 2 groups did not differ in sensation seeking at preadolescence or longitudinally.

Within the family-history-positive cohort, those who did or did not begin using drugs did not differ in impulsiveness or sensation seeking at baseline. However, across adolescence, non-users had greater decreases in overall and motor impulsiveness, and those who initiated drug use had greater increases in sensation seeking.

Discussion: These findings suggest that elevated impulsivity in individuals with substance use disorders may predate problem substance use, and that adolescents with a positive family history have larger relative gaps between impulse control and sensation seeking.

Their increased risk for substance use disorders may be at least partially driven by developmental processes that are common to all adolescents but that are present at a more risky end of the continuum.

Acheson A, Lake S, Bray B, Liang Y, et al: Early adolescent trajectories of impulsiveness and sensation seeking in children of fathers with histories of alcohol and other substance use disorders. *Alcoholism: Clinical and Experimental Research* 2016; doi 10.1111/acer.13235. From the University of Texas Health Science Center at San Antonio; and The Pennsylvania State University, State College, PA. **Funded by the National Institute on Drug Abuse and the NIMH. The 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.

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.

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

Standardized Mean Difference: The difference between two normalized means - i.e. the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales.

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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CHILD & ADOLESCENT PSYCHIATRY ALERTS

ADHD, Bullying, and Psychosis.....	67
Disruptive Behavior: Neurobiology	70
Multifamily Treatment for Anorexia	69
Negative Symptoms and Cognitive Function.....	68
Reference Guide	72
Toddler Aggression: Brief Intervention.....	71

Volume XVIII / December 2016 / Number 12

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ADHD, Bullying, and Psychosis

According to an analysis of data from a longitudinal study, in children with combined-type ADHD, bullying (both as victim and perpetrator) contributes to the development of psychotic experiences during adolescence. Psychotic experiences are a known risk factor for both psychotic and nonpsychotic disorders in later life. To avert these consequences, children with ADHD should be routinely screened for bullying and undergo interventions aimed at bullying prevention.

Methods: Data were analyzed from the Avon Longitudinal Study of Parents and Children, a British study of children born in 1991 or 1992. The present sample consisted of >8000 participants who had data available on mental status at age 7.6 years. Childhood trauma, another potential mediator of the link between ADHD and psychotic symptoms, was assessed using checklists completed on multiple occasions by parents when children were between 6 months and 11 years old. Bullying was assessed at about age 11 years using the Bullying and Friendship Interview Schedule, which measures overt bullying and bullying by exclusion and whether the child was a pure victim, pure bully, or bully/victim. At a mean age of nearly 13 years, participants were interviewed using the semi-structured Psychosis-Like Symptom Interview. The relationships among all of these variables were tested using a series of analyses adjusted for gender, familial schizophrenia, obstetric complications, and IQ, all factors that have been associated with ADHD and psychotic disorders. The analysis was repeated with simple phobia as the primary risk factor, to test whether relationships were specific to ADHD or a shared feature of childhood mental-health disorders.

Results: The associations between combined-type ADHD and traumatic events, bullying, and psychotic experiences were all significant. (See table, next page.) Children with ADHD had not only a higher risk of psychotic experiences by age 12 years, but higher risk of experiencing a traumatic event or of being involved in bullying. Both traumatic events and bullying were linked with a higher risk of psychotic experiences.

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Associations between ADHD, traumatic events, bullying, and psychotic experiences		
Exposure	Outcome	Adjusted Odds Ratio*
ADHD	Psychotic experiences	3.36
ADHD	Traumatic events	2.20
ADHD	Bullying	3.64
Traumatic events	Psychotic experiences	1.57
Bullying	Psychotic experiences	2.00

According to an analysis of the small group of children with ADHD who had experienced both trauma and psychotic experiences, there was no evidence that trauma mediated the relationship between the other 2 variables. In contrast, 9 of the 14 children (64%) who had both ADHD and psychotic-like experiences were also involved in bullying. While bullying accounted for about 40% of the relationship in the adjusted model, it did not reach statistical significance ($p=0.06$). The analysis based on specific phobia found a relationship with psychotic-like experiences but no increased risk for involvement in bullying.

Discussion: There are several possible explanations for the mediating role of bullying. Children with ADHD may be more likely to bully others (due in part to impulsivity and their need for immediate rewards) and to be victims of bullying (because they tend to lack friends for support). Social exclusion appears to promote the manifestation of psychotic ideas. This process is accompanied by anxiety, depression, and negative beliefs about oneself. The authors suggest that preventing bullying in children with combined-type ADHD could reduce the risk of adolescent psychotic experiences by up to 50%.

Hennig T, Jaya E, Lincoln T: Bullying mediates between attention-deficit/hyperactivity disorder in childhood and psychotic experiences in early adolescence. *Schizophrenia Bulletin* 2016; doi 10.1093/schbul/sbw139. From the University of Hamburg, Germany. **Funded by the UK Medical Research Council; and other sources. The authors declared no competing interests.**

*See Reference Guide.

Negative Symptoms and Cognitive Function in Schizophrenia

In a study in drug-naive patients with first-episode schizophrenia, neurocognitive deficits were extensive and were correlated with the severity of negative symptoms. The relationship was particularly strong in adolescents.

Background: The study was conducted to characterize negative symptoms and neurocognitive deficits in patients with first-episode schizophrenia and to follow up on the suggestion that the 2 may be more closely related in adolescents, due to not-yet-complete development of their prefrontal cortex. The study was conducted in a Chinese hospital and restricted to members of the Han ethnic group because of the belief that different ethnic groups have different cognitive abilities.

Methods: Study subjects were 92 patients with first-episode schizophrenia, of whom 33 were adolescents (aged 13–17 years), as well as a control group of 57 healthy volunteers from the community. All participants were administered a battery of neurocognitive tests that are typical of those used in patients with schizophrenia. Psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS), Chinese version, using a 5-factor model based on 9 items.

Results: When evaluated, adolescents had a mean illness duration of 10 months and adults 11 months. The first-episode patients showed significantly poorer performance than controls on most elements of 3 of the neurocognitive tests: Wisconsin Card-Sorting (which measures executive function), Trail Making (visual attention and task switching), and Stroop Color-Word (selective attention, cognitive flexibility, and processing speed). Overall results on the Continuous Performance Test (of sustained and selective attention) did not differ from the control group, although patients made more perseverative errors. In an analysis that was controlled for subjects' level of education, the PANSS negative factor score was significantly correlated with 12 of a possible 16 neurocognitive items measuring executive function; visual, selective, and sustained attention; visual search and processing speed; and cognitive flexibility ($p < 0.05$ for all).

Discussion: Evaluation of neurocognitive deficits is both complex and time consuming. The present results suggest that in adolescents with first-episode schizophrenia, PANSS negative symptom scores may be an easily obtained indicator of these deficits.

Huang M, Huang Y, Yu L, Hu J, et al: Relationship between negative symptoms and neurocognitive functions in adolescent and adult patients with first-episode schizophrenia. *BMC Psychiatry* 2016; doi 10.1186/s12888-016-1052-x. From Zhejiang University; and other institutions, Hangzhou, China. **Funded by the China National Clinical Research Center for Mental Health Disorders; and other sources. The authors declared no competing interests.**

Multifamily Treatment for Anorexia Nervosa

In a randomized trial, multifamily therapy sessions were a useful addition to eating-disorder-focused family therapy in adolescents with anorexia nervosa.

Methods: The study was carried out at 6 specialist eating-disorder clinics in the U.K. Eligible families had an adolescent, aged 13–20 years, who fulfilled DSM-IV criteria for anorexia nervosa or eating disorder NOS, restricting type, and whose body mass index (BMI) was $< 86\%$ of age- and gender-specific medians or who had lost $\geq 15\%$ of their body weight in the prior 3 months. The study excluded those who were at serious medical risk from weight loss. Families were randomly assigned to receive either manualized family therapy for anorexia nervosa (FT-AN) or multifamily therapy. Multifamily therapy was based on the same principles as FT-AN but also included individual family sessions scheduled as needed. In addition, groups of 5–7 families met with the aim of creating a sense of solidarity, reducing stigmatization, learning from each other, mutual support, and cross-family exercises. Multifamily therapy was provided in an intensive 4-day program, followed by 6 single-day meetings at regular intervals. Both treatments were provided over 12 months by therapists routinely practicing in the participating clinics. At 12 months, patients were rated as having a good outcome (i.e., weight $> 85\%$ of the median BMI, menstruating, and no bulimic symptoms), an intermediate outcome (i.e., weight $> 85\%$ of the median BMI but are either not menstruating or have occasional bulimic symptoms) or a poor outcome (i.e., weight $< 85\%$ of the median BMI or frequent bulimic symptoms).

Results: A total of 167 adolescents (mean age, 16 years; 91% girls or young women) took part in the study. At baseline, average BMI was 78% of the age- and gender-specific median and the median illness duration was 7 months. At 12 months, outcomes were good in 25% of the FT-AN group and 43% of the multifamily therapy group. Outcomes were intermediate in 33% of both groups. Odds of a good or intermediate outcome were significantly higher with multifamily therapy (odds ratio, * 2.55; $p = 0.018$). At the 18-month follow-up (i.e., 6 months after the end of therapy) the odds of a good or intermediate response remained 2-fold higher with multifamily therapy but were no longer statistically significant. At 12 months, the treatment groups did not differ in average BMI, eating-disorder psychopathology, depression, or

self-esteem; but by 18 months, patients who received multifamily therapy had reached a significantly higher percentage of the median BMI than the FT-AN group ($p=0.01$). Excluding boys and the girls who were taking contraceptives, about half of the FT-AN group and somewhat more than half of the multifamily therapy group began menstruating.

A total of 9 families in each group discontinued treatment before 3 months. Contrary to expectations, patients who received multifamily therapy did not attend fewer as-needed single-family therapy sessions than the FT-AN group: about 19 in both groups. About half of participants completed a patient satisfaction questionnaire. Of these, >80% of both parents and young people reported moderate-to-high satisfaction with their therapy. Satisfaction with the 2 treatments did not differ.

Discussion: FT-AN is a well-established treatment, supported by numerous randomized trials. About 10–20% of patients who receive it require more intensive treatment. In this study, the multifamily therapy arm also included elements of FT-AN, but other services have provided it as a stand-alone treatment or as part of day care or inpatient treatment. The present study reflects routine clinical practice by available clinicians and includes a highly representative group of patients.

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

Eisler I, Simic M, Hodsoll J, Asen E, et al: A pragmatic randomised multi-centre trial of multifamily and single family therapy for adolescent anorexia nervosa. *BMC Psychiatry* 2016; doi 10.1186/s12888-016-1129-6. From King's College London, U.K.; and other institutions. **Funded by the U.K. Health Foundation. The authors declared no competing interests.**

*See Reference Guide.

Neurobiology of Disruptive Behavior

A meta-analysis of functional MRI (fMRI) studies found a consistent pattern of brain dysfunction in areas that mediate reward-based decision-making in young people with disruptive behavior disorders.¹

Methods: A comprehensive literature search identified whole-brain fMRI studies in children and adolescents with disruptive behavior disorders (i.e., conduct disorder and oppositional defiant disorder). Studies were excluded if they lacked a control group or if they were limited to specific brain regions of interest. Sub-meta-analyses were conducted of "hot" executive functions (i.e., motivationally and emotionally significant tasks), "cool" executive functions (i.e., more abstract tasks), and emotion processing. A separate sub-analysis was conducted in subjects with disruptive behavior disorder with psychopathic traits. Effects of participant gender, age, medication, and ADHD comorbidity were also examined.

Results: The analyses were based on 24 fMRI studies in 338 young people with disruptive behavior disorders and 298 controls. Case patients had a mean age of 15 years (range of study means, 12–18 years), and 80% were boys. A total of 108 youths had psychopathic traits. The rate of ADHD comorbidity was >50% in the majority of studies.

Overall, the study subjects with disruptive behavior disorders showed significantly decreased activation in a cluster of several regions (see table, next page), and no areas of significantly increased activation. Differences from healthy controls in hot, cold, and emotional cognitive subdomains are shown in the table, as are differences in subjects with psychopathic traits. Effect sizes for the differences were small but highly statistically significant, with most p values <0.00005. Male gender was associated with decreased activation (i.e., more severe dysfunction) in some areas, as was increasing age; medication was associated with increased activation; and ADHD comorbidity had no effect.

fMRI differences between youths with disruptive behavior disorder and healthy controls		
Comparison	Brain Region	Activity Level (compared with healthy controls)
Main Meta-Analysis	Rostro-dorsal anterior cingulate cortex/medial prefrontal cortex/supplementary motor area	Decreased
	Ventral caudate	Decreased
Hot Executive Functions	Dorsal anterior cingulate cortex/dorso-medial prefrontal cortex/supplementary motor area	Decreased
	Right dorsal caudate	Increased
Cool Executive Functions	Right superior/middle temporal gyrus/posterior insula/putamen	Decreased
Emotion Processing	Right dorsolateral prefrontal cortex	Decreased
	Left temporal pole	Decreased
Subgroup Analysis: Psychopathic Traits	Hypothalamus/thalamus/ventromedial prefrontal cortex/ventral striatum	Decreased
	Rostral dorsolateral prefrontal cortex	Increased
	Right dorsal (caudate)	Increased

Discussion: Young people with disruptive behavior disorders appear to have the most consistent deficits in closely interconnected regions involved in top-down regulation of motivation and affect. These regions form part of a pathway modulating reward processing, reward-based decision making, and motivation control. The results of the present meta-analyses suggest dysfunctional reward-based decision making is key to conduct disorder and is more common than perturbed empathy or threat sensitivity. Different neurologic mechanisms may be involved in conduct disorder with and without psychopathic traits.

Editorial.² This study casts a spotlight on the discussion of categorical versus dimensional definitions of psychiatric disorders. Differences between affected youths and healthy controls in the main meta-analysis were driven primarily by hot executive function fMRI studies. The study authors suggest this finding supports a categorical approach. However, deficits in hot executive function—specifically reduced reward responsiveness—are also seen in other disorders, including ADHD and depression.

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

¹Alegria A, Radau J, Rubia K: Meta-analysis of fMRI studies of disruptive behavior disorders. *American Journal of Psychiatry* 2016;173 (November):1119–1130. From Kings College London, UK; and other institutions. **Funded by Action Medical Research; and the other sources. One study author disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

²Blair J: The neurobiology of disruptive behavior disorder [editorial]. *American Journal of Psychiatry* 2016;173 (November):1073–1074. From the NIH, Bethesda, MD. **The author declared no competing interests.**

*See Reference Guide.

Brief Parenting Program for Toddler Aggression

A shortened version of a Triple-P group parenting program had moderate effects on toddler aggression and may be useful as part of a stepped-care approach.

Methods: Study participants, recruited via a community media campaign, were families with a child, aged 2 or 3 years, whose aggressive behavior concerned the parents. Children were required to have a score 1 standard deviation above the mean on the parent-reported Physical Aggression Scale for Early Childhood scale. The standard intervention was the Level 4 Group Triple P Program, consisting of 4 group sessions (2 hours each) and 4 telephone sessions (20 minutes each), delivered over 8 weeks. The brief intervention was the Level 3 Triple P Parent Discussion group focusing on managing fighting and aggression, which consisted of a single

2-hour group session and 2 telephone sessions (20 minutes each). This shorter program taught fewer parenting skills—8 versus 17—and included minimal time for role-play. A third group of families was randomly assigned to a waiting list.

Results: A total of 69 families participated in the study. The group included only 4 single-parent families, which by chance were all included in the wait-list control group. At baseline, 26% of children were in the clinical range on the Aggressive Behavior scale of the Child Behavior Checklist (CBCL), and another 25% were in the borderline range. Participants in the standard program spent an average of 8 hours and 23 minutes participating, compared with 2 hours and 36 minutes in the brief program.

As expected, parents who received the standard intervention reported better results than the waitlist group across most assessment measures, with large improvements in mother-rated child aggression and dysfunctional parenting, observed child aversive behavior, and mother- and partner-rated parental self-efficacy. Effect sizes were generally large. Results of the shortened program were mixed. Compared with the waitlist group, only the reduction in the parenting behavior of verbosity was significantly greater. Other changes in the brief-intervention group were generally positive, but with small-to-medium effect sizes. However, the study was underpowered to detect smaller effects. Both mothers and partners reported greater satisfaction with the standard intervention than the brief intervention.

All 11 children who were in the CBCL clinical or borderline range of aggression at baseline were in the normal range following the standard intervention, compared with 9 of 12 children who received the brief program and 4 of 8 waitlisted children. There were no significant differences between the standard and brief intervention groups on any outcome measure at 6 months.

Discussion: Aggression that is developmentally excessive in toddlers is often persistent throughout childhood. Physical aggression is a core feature of disruptive behavior disorders. Most studies of parenting programs have targeted general externalizing behaviors, not aggression specifically. The present study provides support for the standard Triple P program in reducing aggression. Unfortunately, lengthy parent training programs are limited by low participation and high attrition. These study results suggest clinicians should be cautious in delivering an abbreviated program as a stand-alone intervention. However, it may be useful as a first stage in a stepped-care model, provided that more intensive interventions are available to families that do not benefit from the brief intervention.

Tully L, Hunt C: A randomized controlled trial of a brief versus standard group parenting program for toddler aggression. *Aggressive Behavior* 2016; doi 10.1002/ab.21689. From the University of Sydney, Australia. **Funded by the New South Wales Institute of Psychiatry; and other sources. The authors declared no competing interests.**

Reference Guide

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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2016 Index

A

adaptive skills, 64
ADHD, 1, 7, 11, 17, 21, 22, 25, 29, 31, 37, 38, 51, 64, 67
adolescent brain development, 49
adverse effects, 9, 35, 53
Adzenys XR, 7
aggression, 14, 25, 26, 71
agomelatine, 51
alcohol use, 50
amitriptyline, 40
anorexia nervosa, 69
antipsychotics, 10, 23, 39, 47
anxiety, 43, 48, 62
asenapine, 8
atomoxetine, 31, 33, 47
autism, 16, 32, 44, 52

B

behavioral therapy, 31
beta-2-agonists, 16
bipolar disorder, 3, 4, 8, 19, 27
bone mass, 55
brain-imaging, 37
bright light therapy, 2
bullying, 67
buprenorphine, 49
buspirone, 16

C

cannabis, 5
childhood trauma, 27
citalopram, 40
clomipramine, 40
clonidine, 29, 32, 47
cognitive behavioral therapy, 11, 15, 28, 31, 43, 46, 63
cognitive psychophysiological treatment, 58
compliance enhancement, 13
conduct disorder, 47

D

D-cycloserine, 46
depression, 2, 15, 28, 40, 41, 53, 62, 63
desipramine, 40
dexmethylphenidate, 29, 51
diabetes, 23
dialectical behavioral therapy, 13
disruptive behavior disorder, 20, 25, 62, 70
disruptive mood dysregulation disorder, 29
divalproex, 47
duloxetine, 40

E

eicosapentaenoic acid, 3
energy drinks, 45
escitalopram, 40
extended-release amphetamine–dextroamphetamine, 31

F

Facotik, 58
family intervention, 13

fatty acids, 3
Fetal exposure, 16
fluoxetine, 40
fracture, 35

G

group therapy, 13, 22
guanfacine, 1, 32, 51

I

imipramine, 40
Impulsive aggression, 26
impulsivity, 65
individual family psychoeducational psychotherapy, 4
inositol, 3
interpersonal therapy, 63
irritability, 22

L

lisdexamfetamine, 31
Lithium, 47

M

mentalization-based therapy, 13
metformin, 52
methadone, 49
methylphenidate, 31, 38, 47, 51
mindfulness-based cognitive therapy, 61
mindfulness instruction, 61
mindfulness meditation, 17
mirtazapine, 40
mixed amphetamine salts, 7
molindone, 47
montelukast, 9
multifamily therapy, 69

N

naltrexone, 49
nefazodone, 40
negative symptoms, 68
nortriptyline, 40

O

obsessive-compulsive disorder, 46
olanzapine, 39
opioid addiction, 49

P

parent training, 20, 62
parental accommodation, 48
parental depression, 57
Parenting Wisely, 62
paroxetine, 40
planned aggression, 26
psychotic experiences, 67
psychotic symptoms, 7
puberty, 41

Q

quality of life, 21
quetiapine, 39, 47

R

repetitive transcranial magnetic stimulation, 56
risperidone, 39, 47

S

salivary biomarkers, 32
schizophrenia, 5, 68
self-harm, 13
sertraline, 40, 43, 53
severe mood dysregulation, 22
skills training, 31
SNRIs, 43
SSRIs, 35, 43
stimulants, 7, 25, 29, 55, 64

substance use disorders, 65
subsyndromal bipolar disorder, 4
suicidality, 14
suicide, 33, 34, 53, 59
suicide prevention, 34

T

tics, 29, 58
token-economy system, 11
Tourette's Disorder, 29, 58
treatment-resistant depression, 56
Triple P Program, 62, 71

V

venlafaxine, 40

W

weight gain, 52