# CHILD & ADOLESCENT PSYCHIATRY ALERTS 2018 VOLUME 20

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## Lurasidone in Bipolar Depression

In a manufacturer-sponsored, placebo-controlled trial in young patients with bipolar depression, treatment with lurasidone produced significant and clinically meaningful improvement in depression. Effects on weight and metabolic parameters were minimal.

***Methods:*** Participants in this international study were young people, aged 10–17 years, with bipolar I disorder who were currently experiencing a major depressive episode of 1–12 months' duration. Participants were required to have a baseline score of ≥45 on the Children's Depression Rating Scale-Revised (CDRS-R) and ≤15 on the Young Mania Rating Scale (YMRS). Patients with rapid cycling (i.e., ≥4 but ≤8 mood episodes in the prior 12 months) or comorbid ADHD and receiving stable medication were not excluded from the study. Following a ≤3-week screening period, which included a taper of previous medications, patients were randomly assigned to double-blind treatment with lurasidone, flexibly dosed at 20–80 mg/day, or placebo. Concomitant stable stimulants for ADHD were permitted. The primary efficacy outcome was change from baseline to week 6 in CDRS-R total score. The key secondary outcome was change from baseline in the Clinical Global Impression–Bipolar Severity (CGI-BP-S) scale. Response was defined as a ≥50% reduction in the CDRS-R (after a reduction of 17 points to adjust for the scale's range), and remission as a composite of a CDRS-R score ≤28, a YMRS score ≤8, and a CGI-BP-S depression item score ≤3.

***Results:*** A total of 343 patients (mean age, 14 years; 51% boys) were included in the primary efficacy analysis, including 39 who were taking stimulant medication for ADHD. The mean lurasidone dosage was 32.5 mg/day, but >50% of patients received the lowest dosage. More than 90% of patients completed the study.

Lurasidone was associated with a larger reduction in the CDRS-R total score than placebo (21 vs 15 points; $p<0.0001$; effect size,* 0.45). Changes from baseline in the CGI-BP-S averaged 1.49 and 1.05 points, respectively ($p<0.0001$; effect size, 0.44). Lurasidone appeared to be significantly more effective in reducing the CDRS-R in adolescents (aged 15–17 years)

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than in children (aged 10–14), largely due to a higher placebo response rate in the younger patients. More patients met response criteria with lurasidone than with placebo (60% vs 37%; p<0.0001; number needed to treat,* 5). Rates of remission (26% vs 19%; number needed to treat, 14) did not differ statistically between the groups. Lurasidone was also superior to placebo for other secondary measures, including anxiety, global functioning, and quality of life.

The most frequent adverse effects of lurasidone were nausea and somnolence. Rates of suicidal ideation were low and similar in the 2 groups. Compared with placebo, lurasidone was not associated with higher rates of emergent mania or hypomania (1.7% vs 2.3%), akathisia (2.9% vs 3.5%), or other extrapyramidal symptoms (2.3% vs 1.7%). Neurocognitive tests showed no deterioration in patients taking lurasidone. Changes in body weight and body mass index were similar in the 2 groups.

***Discussion:*** There are few pharmacotherapy options for treating bipolar depression in children and adolescents. Recent clinical trials found quetiapine ineffective, and while fluoxetine–olanzapine is FDA approved for this indication, it is associated with high rates of intolerable adverse effects and clinically significant weight gain. These results, although they require replication, suggest that lurasidone may be a safe and effective option for this patient population.

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

DelBello M, Goldman R, Philips D, Deng L, et al: Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. *Journal of the American Academy of Child and Adolescent Psychiatry* 2017;56 (December):1015–1025. From the University of Cincinnati College of Medicine, OH; and Sunovion Pharmaceuticals, Marlboro, MA, and Fort Lee, NJ. **Funded by Sunovion Pharmaceuticals. All 6 study authors disclosed financial relationships with commercial sources including Sunovion.**

***Common Drug Trade Names*: fluoxetine–olanzapine—*Symbyax*; lurasidone—*Latuda*; quetiapine—*Seroquel***

***See Reference Guide.**

## Suicide Risk in Sexual Minority Adolescents

Lesbian, gay, bisexual, and questioning adolescents were up to 3 or more times more likely to report suicidal behaviors than their heterosexual peers, according to the 2015 National Youth Risk Behavior Survey.

***Methods:*** The survey was based on a representative sample that includes adolescents from all U.S. states and both public and private high schools. Students responded anonymously on computer-scannable paper questionnaires completed at school. They were asked whether, in the previous year, they had seriously considered suicide, planned suicide, or attempted suicide. Relative risks in comparison to heterosexual adolescents were calculated overall and by sexual minority subgroup and gender. The risk estimates were adjusted to represent the U.S. general adolescent population.

***Results:*** Of a total of >15,600 adolescents surveyed, 89% identified themselves as heterosexual, 2% identified as lesbian, 6% as bisexual, and 3% as questioning. Among sexual minority youth, risks of all 3 types of suicidal behavior were elevated. Compared with heterosexual youth, adjusted risk ratios* in the minority groups were 2.45 for seriously considering suicide, 2.59 for planning suicide, and 3.37 for suicide attempt. Except for suicide attempts in the questioning group, in both heterosexuals and sexual minorities, risks of each type of behavior were generally higher in female than male adolescents. By minority subgroup, risks of each type of behavior were elevated in lesbian, gay, bisexual, and questioning adolescents, relative to heterosexuals. Rates of a suicide attempt in the past year ranged from about 15–23% in subgroups of sexual minority males and 12–34% in subgroups of sexual minority females.

***Discussion:*** Nationally representative studies of suicide risk in sexual minority adolescents are rare and not sufficiently recent or detailed. Despite its limitations, the present survey suggests a need for research on effective suicide prevention in sexual minorities, as well as vigilance on the part of clinicians.

Caputi T, Smith D, Ayers J: Suicide risk behaviors among sexual minority adolescents in the United States, 2015 (letter). *JAMA* 2017;318 (December 19):2349–2351. From the Wharton School, University of Pennsylvania, Philadelphia; and other institutions. **Funded by the Joseph Wharton Scholar program; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

## Adolescent Cannabis and Hypomania

Cannabis use during adolescence was found to be an independent risk factor for hypomania symptoms in young adults in a population-wide cohort study. Cannabis use was also suggested as a candidate mechanism linking childhood abuse with later hypomania.

***Methods:*** The Avon Longitudinal Study of Parents and Children birth cohort consisted of >14,000 children born in 1991–1992 in the county of Avon in southwestern England. Children were assessed annually in the clinic with interviews and physical and psychological tests. Cannabis use was assessed by participant report at age 17 years. Hypomania symptoms were measured when participants were aged 22–23 years using a mailed questionnaire, the 32-item Hypomania Checklist Questionnaire. The questionnaire was developed as a screening test for bipolar II disorder but has been validated for subclinical symptom assessment. Hypomania required a symptom threshold of 14 out of 32 during any lifetime episode of feeling high or "hyper," with negative consequences and ≥2–3 days of symptoms. The statistical model included additional variables such as family risk factors and physical and sexual abuse up to the age of 7 years (reported by the mother), adolescent-reported use of alcohol and illicit drugs, and psychotic and depressive symptoms in late adolescence.

***Results:*** Data on hypomania symptoms in young adulthood were available for 3370 participants. The final analysis was weighted to compensate for the high attrition rate. After adjustment for potential confounders, cannabis use was associated with significantly elevated risk of hypomania in young adulthood. (See table.) Frequent cannabis use predicted hypomanic symptoms as well as depression and psychosis. A path analysis* showed that cannabis use was an independent risk factor for hypomania and also mediated the associations of male gender and childhood abuse with hypomania.

**Adjusted associations between cannabis use at age 17 years and hypomanic symptoms at ages 22–23 years†**

| Cannabis Use | Odds Ratio* |
|---|---|
| Any cannabis use vs no cannabis use | 1.42 |
| Frequent use (≥2–3 times/week) vs less than weekly | 2.21 |

†Adjusted for psychotic symptoms, depression, other drug use, hazardous alcohol use, gender, family adversity, and early childhood physical or sexual abuse

***Discussion:*** The few prospective studies linking cannabis use with mania have focused on adult samples and have not always controlled for psychotic symptoms. The present finding of an association between adolescent cannabis use and later hypomania after controlling for alcohol and drug use and psychotic symptoms, along with the dose-response relationship, suggest the association may be directly causal. The authors suggest several potential mechanisms for the association: Alterations of reward system sensitivity via increasing dopaminergic signaling could underlie the association; harmful use of cannabis is more frequent in men than in women, and its use in men may be more important in the pathway

to hypomania; childhood physical and sexual abuse are indirectly associated with hypomania via increased risk of cannabis use.

Marwaha S, Winsper C, Bebbington P, Smith D: Cannabis use and hypomania in young people: a prospective analysis. *Schizophrenia Bulletin* 2017; doi 10.1093/schbul/sbx158. From the University of Warwick, U.K.; and other institutions. Funded by the UK Medical Research Council; and other sources. One of 4 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.

***See Reference Guide.**

## Group Metacognitive Therapy for GAD

In an uncontrolled trial, group metacognitive therapy was an effective, acceptable treatment for generalized anxiety disorder in children.[1] Treatment effects were comparable to those previously found with cognitive behavioral therapy (CBT), the established therapy for childhood anxiety disorders.

***Methods:*** Metacognitive therapy for children (MCT-c) is a manualized program developed by the authors, adapted from MCT for GAD in adults. MCT aims to teach a state of detached mindfulness, in which the patient notices but does not pay attention to worry-inducing negative thoughts. Study participants were self-referred families with a child, aged 7–13 years, who had a primary diagnosis of GAD. The therapy was delivered in 8 weekly 2-hour group sessions with 5–6 children and 3–4 therapists. Parents participated in 2-hour workshops prior to treatment and again 4 weeks into treatment. Children practiced attention training, shifting attention between their thoughts and stimuli in the environment, and detached mindfulness using in-session experiments, field trips, and other activities. Outcomes were assessed at the end of treatment and after 6 months.

***Results:*** Study participants were 22 girls and 22 boys with confirmed GAD. The majority of patients had comorbid disorders; more than half had ≥2 additional diagnoses, usually but not exclusively other anxiety disorders. Half of the families had previously received psychological counseling or therapy for their child's anxiety. None of the children were taking psychotropic medications.

Of the 44 participating families, 43 completed treatment and 4 took advantage of optional booster sessions. At post-treatment, 38 children (86%) no longer met criteria for GAD and 32 (73%) were free of all anxiety disorders. At follow-up, 33 (75%) were free of GAD and 29 (66%) were free of all anxiety disorders. At both endpoints, children showed significant improvement on standardized measures of anxiety, with large effect sizes.* (See table.) Participants showed significant improvement on a validated measure of positive beliefs about the usefulness of worry, negative beliefs about the uncontrollability and dangerousness of worry, need to control thoughts, and cognitive self-consciousness. Cognitive confidence, was unchanged.

**Change from baseline in standardized measures of anxiety**

| Measure | Effect Size | |
|---|---|---|
| | Pretreatment to posttreatment | Pretreatment to 6-month follow-up |
| **Revised Child Anxiety and Depression Scale (RCADS)–child** | 1.20 | 1.26 |
| **RCADS–mother** | 1.29 | 1.28 |
| **RCADS–father** | 0.98 | 0.90 |
| **Penn State Worry Questionnaire for Children** | 0.95 | 1.04 |

***Discussion:*** CBT is a well-established treatment for GAD in children, with an average effect size of 0.74, according to a recent meta-analysis.[2] Controlled trials comparing MCT with CBT appear to be warranted.

[1]Esbjørn B, Normann N, Christiansen B, Reinholdt-Dunne M: The efficacy of group metacognitive therapy for children (MCT-c) with generalized anxiety disorder: an open trial. *Journal of Anxiety Disorders* 2018;53 (January):16–21. From the University of Copenhagen, Denmark. **Funded by the Tryg Foundation; and other sources. The authors did not include disclosure of potential conflicts of interest.**

[2]Ishikawa, S, et al: Cognitive behavioural therapy for anxiety disorders in children and adolescents: a meta-analysis. *Child and Adolescent Mental Health* 2007;12 (4):164–172.

***See Reference Guide.**

## Measuring Patient-Centered Outcomes in ADHD

A systematic review of randomized trials indicates that in patients with ADHD functional impairment and health-related quality of life (HRQoL) generally improve with drug treatment. Effects appear to be larger in children and adolescents than in adults and with stimulants versus non-stimulant medications.

***Background:*** It is now widely acknowledged that treatment of ADHD should aim to improve function and HRQoL, in addition to improving ADHD symptoms. Assessing these outcomes typically relies on completion of a questionnaire by the patient or by a proxy such as a parent or teacher. The 2 outcomes share similarities, but functional impairment is generally considered to be objective and ideally assessed by unbiased methods, while HRQoL is considered to be subjective and best rated by the patient. It is important to use measures that do not merely mirror changes in ADHD symptoms.

***Methods:*** The systematic review included English-language papers, published in peer-reviewed journals, which reported placebo-controlled studies of ADHD medications with analyses of functional outcomes or HRQoL. Study designs could be parallel-group, crossover, treatment initiation, or treatment withdrawal. The reviewers did not formally assess risk of bias, but noted that because the outcomes of interest are usually secondary efficacy measures, they may be less likely to be reported than primary outcomes. Post-hoc analyses were excluded for this reason. A meta-analysis could not be conducted because of the diversity of study designs, populations, medications, and outcome measures. To reduce bias, the analysis reported effect sizes,* with a cutoff of 0.50 as a threshold for clinical relevance.

***Results:*** The analysis was based on 34 studies, 18 in children and adolescents and 16 in adults. A total of 14 investigated stimulants, and 21 investigated non-stimulants. Almost all were short-term, with treatment lasting ≤20 weeks.

HRQoL was proxy-rated by parents in nearly all child and adolescent studies. The most frequently used instrument to measure HRQoL was the Child Health and Illness Profile-Child Edition: Parent Report Form. Children and adolescents with ADHD had substantially reduced HRQoL before treatment, with average scores 1.5–2.0 standard deviations below population norms in domains reflecting achievement and risk taking. Of 12 studies that reported HRQoL, 10 reported improvement in ≥1 domain or summary measure, with the largest improvements in domains related to achievement and risk taking. In the most responsive domains, effect sizes were larger for stimulants (range, 0.54–1.28) than for non-stimulants (range, 0.29–0.87).

Function was often measured using the Weiss Functional Impairment Rating Scale–Parent. Children and adolescents showed fairly consistent improvement in the Family and Learning and School domains. Effect sizes in responsive domains ranged from 0.86 to 1.25 for stimulants and from 0.32 to 0.58 for non-stimulants.

Severity of and improvement in ADHD symptoms were correlated moderately to strongly, but not perfectly, with improvements in function and HRQoL. Improvements were greatest in domains related to school or achievement, risk taking, and interpersonal relationships, the domains with the greatest deficits at baseline. Studies reported larger effect sizes for ADHD symptoms than for HRQoL and functional outcomes.

***Discussion:*** Poor HRQoL and functional impairment relate to ADHD symptoms but are distinct, reflecting the impact of the disorder on patients' daily lives. The results of this analysis suggest that improving function and quality of life should be an important aim of ADHD treatment. They do not, however, address whether improvements in function and HRQoL are directly related to pharmacotherapy, improvements in symptoms, or both.

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

Coghill D, Banaschewski T, Soutullo C, Cottingham M, et al: Systematic review of quality of life and functional outcomes in randomized placebo-controlled studies of medications for attention-deficit/hyperactivity disorder. *European Child and Adolescent Psychiatry* 2017;26 (November):1283–1307. From the University of Melbourne, Australia; and other institutions. **Funded by Shire International GmbH. All 5 study authors disclosed financial relationships with commercial sources.**

***See Reference Guide.**

## Reference Guide

**Effect Size: T**he effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

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

**Odds Ratio:** A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**Path Analysis:** A method employed to determine whether or not a multivariate set of nonexperimental data fits well with a particular (a priori) causal model.

**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.

**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.





***Off-Label Drug Use Statement:*** **Some drugs discussed for specific indications in Child & Adolescent *Psychiatry Alerts* articles may not be approved for labeling and advertising for those indications by the U.S. FDA.**

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## Olanzapine for Restrictive Eating Disorder

Adjunctive low-dose olanzapine (*Zyprexa*) increased eating and weight gain in children and adolescents undergoing treatment for avoidant restrictive food intake disorder (ARFID) at an eating disorders clinic. In this uncontrolled retrospective study, olanzapine was also associated with improvement in mood, anxiety, and cognition.

***Background:*** Unlike other eating disorders, ARFID is not driven by body-image distortion or fear of weight gain. Rather, the food restriction and avoidance tend to be based on extreme sensitivity to the sensory characteristics of food (e.g., taste, texture, smell, temperature) and/or on a conditioned response involving the expectation that a previous negative experience (e.g., choking, difficulty swallowing) will be repeated. The treatment of ARFID generally takes an approach borrowed from other eating disorders. While there is no evidence for pharmacotherapy in ARFID, low-dose olanzapine is arguably the most effective drug treatment for anorexia nervosa.

***Methods:*** The eating disorders program admitted 8 girls and 3 boys with DSM-5 ARFID. All patients had been symptomatic for many years but had not received a formal diagnosis before admission. Of the 11 patients, 9 were given olanzapine after they did not gain ≥1 lb per week with standard treatment in a structured behavioral program, with meal behavior therapy 6 times per day (3 meals, 3 snacks). Other treatments included individual, group, and family therapies, nutrition counseling, and pharmacotherapy. Olanzapine was typically started at 0.625 mg/day, and titrated based on response and tolerability.

***Results:*** The 9 patients (8 girls) who received olanzapine had mean age of 14 years and an average body mass index (BMI) of 15.6, below the 11th BMI percentile for age. Six were below the 5th percentile, and 5 were below the 3rd percentile. The patients who received adjunctive olanzapine were discharged after a mean of 68 days of residential, partial hospital, and intensive outpatient treatment. They received olanzapine for a mean of 53 days, and the average olanzapine dosage at discharge was 2.8 mg/day.

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Average daily weight gain while receiving adjunctive olanzapine was 0.25 lbs, and patients had gained an average of 16 lbs and 3 BMI points by discharge. The BMI-per-age percentile increased to 36 ($p \leq 0.002$, compared with baseline). All patients had a comorbid psychiatric disorder diagnosis on admission. By the time of discharge, patients and their families reported significant improvement in anxiety and depressive symptoms. Cognitive improvement was also noted by parents, therapists, and teachers, with gains in school attendance, participation, and performance. The mean Clinical Global Impression–Severity score decreased from 5.3 (markedly ill) to 3.2 (mildly ill).

***Discussion:*** To the authors' knowledge, there have been no randomized trials of olanzapine or any other pharmacotherapies for ARFID. While the present results are positive, they require replication. The authors emphasize the importance of using low-dose therapy (frequently requiring pill-cutting) and of slow dosage titration.

Brewerton T, D'Agostino M: Adjunctive use of olanzapine in the treatment of avoidant restrictive food intake disorder in children and adolescents in an eating disorders program. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (December):920–922. From the Medical University of South Carolina, Charleston; and the University of South Carolina, Columbia. **Source of funding not stated. The authors declared no competing interests.**

## Pharmacotherapy for Tourette Syndrome

About 80% of children who present with Tourette syndrome (TS) tics at age <10 years will experience a significant decrease in tic frequency and severity during adolescence, with eventual functional recovery by age 18 years. For those who require treatment, comprehensive behavioral intervention for tics (CBIT) is highly effective and should be considered as first-line therapy. Medication is recommended when CBIT is ineffective, inappropriate, or unavailable. However, patients and families should be made aware that medications typically reduce tic symptoms by about 25–50%. The present recommendations are based on published research on drug treatment and on clinical guidelines from Canada and Europe.

***First-Line Pharmacotherapy.*** The alpha agonists clonidine and guanfacine are appropriate first-line pharmacotherapy (after CBIT). Clonidine has been used to treat TS for >30 years and has "moderate" evidence of efficacy along with a benign adverse-effect profile. Evidence supporting a moderate effect of guanfacine for tic reduction is more limited, and the extended-release formulation does not appear to be effective.

***Second-Line Pharmacotherapy.*** The GABA-B receptor agonist baclofen, which is commonly used to treat spasticity, should be considered next-line therapy. However, the quality of its evidence base is weak. The vesicular monoamine transporter-2 inhibitor tetrabenazine (FDA approved for Huntington's chorea) showed promising effects in preliminary studies in patients with TS. Of other agents in the class, deutetrabenazine (also FDA approved for Huntington's chorea) has shown promising results in an open-label trial, and valbenazine is currently under investigation for TS.

***Third-Line Pharmacotherapy.*** Atypical antipsychotics are considered as next-in-line pharmacotherapy in the U.S. (and older neuroleptics elsewhere), with aripiprazole and risperidone the recommended first choices. Aripiprazole is FDA approved for this indication and supported by 2 large clinical trials. Risperidone also has convincing evidence of efficacy and may be helpful in comorbid conditions such as aggression or obsessive-compulsive symptoms, but it requires monitoring for dyskinesias and metabolic effects.

Other agents are being investigated but do not yet have sufficient evidence of efficacy. Cannabinoids have shown promise in preliminary studies and appeal to patients who are seeking a "natural" plant-based treatment. The benzodiazepine clonazepam and the investi-

gational D1/D5 antagonist ecopipam also have had promising initial results. The dopamine agonist pramipexole and the antiemetic metoclopramide have been investigated in the treatment of TS, but they were found to be ineffective.

Quezada J, Coffman K: Current approaches and new developments in the pharmacological management of Tourette syndrome. *CNS Drugs* 2018; doi 10.1007/s40263–017–0486–0. From Children's Mercy Hospital, Kansas City, MO. **Funded by the hospital. One study author disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

***Common Drug Trade Names*: aripiprazole—*Abilify*; baclofen—*Lioresal*; clonazepam—*Klonopin*; clonidine—*Catapres*; deutetrabenazine—*Austedo*; guanfacine—*Tenex*; metoclopramide—*Reglan*; pramipexole—*Mirapex*; risperidone—*Risperdal*; tetrabenazine—*Xenazine*; valbenazine—*Ingrezza***

## Optimal Length of Antidepressant Treatment

Treatment with antidepressants, if response is achieved, should be continued for 9–12 months in children and adolescents with depression and for 6–9 months for those with anxiety disorders, according to a review of treatment guidelines and the limited research literature. If remission does not occur with acute antidepressant treatment, whether combined with psychotherapy, a change of antidepressant should be considered.

Based on current practice guidelines, clinical trial evidence, and specific relapse-prevention strategies, short-term use of SSRIs, particularly fluoxetine (*Prozac*), combined with psychotherapy, is effective in bringing about symptomatic and functional improvement in pediatric depression and anxiety. However, the risk of relapse and recurrence remain high. In adults, evidence-based relapse-prevention strategies include continuation of acute medication, psychotherapy booster sessions, and tailored recurrence-prevention interventions. Evidence is much more limited in the pediatric population; most studies do not extend beyond 12 weeks.

Pediatric treatment guidelines generally focus on acute treatment. For depression, guidelines recommend an evidence-based psychotherapy combined with an SSRI, with dose reevaluation every 4 weeks. Symptomatic improvement should occur by 12 weeks. Recommendations for continued treatment beyond that point conflict and may not have been updated in light of recent research. A typical recommendation, from the American Academy of Child and Adolescent Psychiatry (AACAP), is to continue antidepressant medication for 6–12 months following response to acute treatment. The guideline adds that discontinuation in the summer may be preferable to during the school year and that longer treatment may benefit patients with certain risk factors. (See table.) Studies with long-term follow-up, such as the Treatment for Adolescents with Depression Study, indicate that the response rate continues to increase from treatment week 12 to 36 if accompanied by CBT. Recovery from a major depressive episode generally occurs within 1–2 years, but recurrence is common and frequently occurs 6–12 months following the end of acute treatment.

**Factors associated with a lower likelihood of response or remission in long-term treatment of anxiety and depression in children and adolescents**

| Depression | Anxiety |
|---|---|
| More prior depressive episodes | Older Age |
| Residual symptoms after treatment* | Female gender |
| Greater family levels of expressed emotion | Minority status |
| Perceived family conflict | Baseline symptom severity |
| Non-response to acute therapy | Lower socioeconomic status |
| Female gender* | Social anxiety disorder |
| | Negative life events |
| | Comorbid internalizing disorders |

* Based on adult data or unpublished research.

The AACAP guidelines for acute treatment of anxiety, which have not been updated in more than a decade, recommend evidence-based psychotherapy, such as CBT for mild anxiety and SSRIs for moderate-to-severe anxiety disorders. Only 1 recommendation, based on a >15-year-old expert opinion paper, addresses long-term therapy for anxiety. This report

recommends antidepressant discontinuation during a low-stress period, at least 1 year following symptomatic response. The few published clinical trials suggest antidepressant therapy for anxiety continues to be effective for up to 6–9 months. However, many clinicians choose to treat for a full year, largely based on a discontinuation study in adults.

There is no evidence suggesting harm from long-term use of SSRIs in the absence of adverse effects. Based on the limited evidence, the authors suggest that for young patients with depression or anxiety, treatment and its discontinuation should be based on individual patient's risk factors for poor prognosis.

Hathaway E, Walkup J, Strawn J: Antidepressant treatment duration in pediatric depressive and anxiety disorders: how long is long enough? *Current Problems in Pediatric and Adolescent Health Care* 2017; doi 10.1016/j.cppeds.2017.12.002. From the Indiana University School of Medicine, Indianapolis; and other institutions. **Source of funding not stated. Two of 3 study authors disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

## Multisystemic Therapy for Antisocial Behavior

In a large randomized trial, multisystemic therapy (MST) showed no advantage over usual care in adolescents with antisocial behavior. Multiple studies from the U.S. have suggested MST may improve outcomes of antisocial and offending behavior in young people; but the present study, from the U.K., indicates that this result may not be generalizable. Adolescents' parents rated MST favorably at first, but these ratings were transient and not reflected in objective measures of behavior; MST had some harmful effects; and the treatment was not a cost-effective enhancement of usual care.

***Methods:*** The study was conducted at 9 MST pilot centers in England. The centers had ≥12 months' experience with the treatment. Participants, aged 11–17 years, were referred from a variety of sources and were required to show ≥3 severity criteria for antisocial behavior, including past difficulty in several settings and any of 5 general inclusion criteria: persistent and enduring (weekly for ≥6 months), DSM-IV conduct disorder with no response to treatment, multiple warnings and ≥1 conviction, permanent expulsion from school, or risk of harm to self or others. Half of participants were randomly assigned to receive MST followed by treatment as usual. MST consisted mainly of work with the adolescent's caregiver and was provided by therapists who met with the family 3 times a week for 3–5 months. The MST intervention used techniques from cognitive behavioral therapy, behavioral therapy, and strategic and structural family therapy to improve parenting skills, enhance family relationships, increase social-network support, improve communication, encourage school attendance, and reduce the adolescent's contact with delinquent peers. The remaining patients received only treatment as usual, which was nonstandardized but generally multicomponent and no less intensive than MST. The primary study outcome was the proportion of participants placed in out-of-home care at 18 months. Study investigators were blind to participants' treatment allocation.

***Results:*** A total of 684 families participated in the study, of whom 72% were available for assessment at 18 months. More than 80% of adolescents had a diagnosis of any conduct disorder, 65% had persistent and enduring violent and aggressive behavior, 9% had ≥1 conviction plus multiple warnings, 26% had been expelled from school, and 10% posed a danger to themselves or others.

MST had no protective effect on the rate of out-of-home placements at 18 months, which was 13% versus 11% for care as usual. MST also did not delay the time to the first criminal offense; and at 18 months, the mean number of offenses was significantly higher in the MST group. Minor improvement, compared with usual care, in self- and parent-reported antisocial

behavior and attitudes and in self-reported substance misuse were reported at 6 months, but this effect did not last. Parents in the MST group reported improvements in multiple facets of parenting behavior, but adolescents' reports did not mirror these changes. Detrimental effects of MST on out-of-home placement were strongest in patients with younger age at onset of conduct problems, low baseline levels of callous and unemotional traits, and fewer delinquent peers. The mean total service costs over 18 months were about $42,700 for treatment as usual and about $39,620 for MST.

***Discussion:*** Overall, it appears that parents benefited more from MST than adolescents. This parental improvement may translate into long-term behavioral benefits in adolescents over a longer time frame than 18 months. It is possible that MST increased risk of illegal activity in young people initially at low risk for criminal offenses by sensitizing them to the possibility. It is also possible that the failure of this study to replicate results of the U.S. studies could be due to greater effectiveness of treatment as usual in the U.K.

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

Fonagy P, Butler S, Cottrell D, Scott S, et al: Multisystemic therapy versus management as usual in the treatment of adolescent antisocial behaviour (START): a pragmatic, randomised controlled, superiority trial. *Lancet Psychiatry* 2018;5 (February):119–133. From University College London, U.K.; and other institutions. **Funded by the Department for Children, Schools and Families and the Department of Health. No study author disclosed financial relationships with commercial sources.**

***See Reference Guide.**

## Medication Algorithm for Youth At-Risk of Bipolar Disorder

As part of a randomized trial of psychosocial interventions, researchers developed a pharmacological treatment algorithm for children and adolescents at high risk for bipolar disorder.[1] The algorithm guided background medication in study participants with mood symptoms and a first-degree relative with bipolar disorder, a group for whom treatment guidelines are lacking.

***Methods:*** The randomized trial, whose main results were previously reported,[2] compared a 4-month family-focused therapy with an educational control therapy in 40 young people at high familial risk of bipolar disorder. Study participants were aged 9–17 years; had a diagnosis of bipolar disorder NOS, major depressive disorder, or cyclothymia; had active mood symptoms; and had a first-degree relative with bipolar I or II disorder. The study's pharmacotherapists developed the algorithm based on the few available treatment studies, existing guidelines for treating syndromal bipolar disorder and depression in young people, and, in areas where these sources were not available, expert opinion and consensus among the study psychiatrists. During the study, medication selection was based on collaborative decision-making by clinicians, patients, and family members using the algorithm and was monitored by a pharmacotherapy oversight committee. Physician adherence to the algorithm was rated by the study's supervising psychiatrists.

***Results:*** The initial step in the algorithm is a determination of whether medication is necessary, followed if appropriate by starting pharmacotherapy or optimizing existing medication, with the goal of stabilizing symptoms to the point that the patient can participate in therapy.

Although conversion to bipolar disorder was not evaluated in the study, no patient experienced antidepressant- or stimulant-induced mania. Physician adherence to the treatment algorithm was high, with only 2% of study visits involving nonadherent prescribing and 14% of visits involving partially adherent prescribing.

| Medication Recommendations for Patients at High Risk for Bipolar Disorder | |
|---|---|
| Unipolar Depression | Bipolar Disorder NOS |
| **No history of antidepressant-induced mania**<br>**First-line treatments:** citalopram, bupropion, sertraline, or escitalopram<br>**Second-line treatment:** venlafaxine, duloxetine, lamotrigine<br>**History of antidepressant-induced mania**<br>**First-line treatment:** lamotrigine<br>**Second-line treatment:** lithium or quetiapine<br>**Comorbid ADHD, not receiving antidepressant therapy**<br>**First-line treatment:** bupropion<br>**Comorbid ADHD, receiving antidepressant therapy**<br>**First-line treatment:** methylphenidate or mixed amphetamine salts<br>**Second-line treatment:** atomoxetine | **Experiencing manic/mixed symptoms**<br>**First-line treatment:** aripiprazole,[±] quetiapine,[±±] risperidone, lithium[±±±]<br>**Second-line treatment:** lithium, divalproex, lamotrigine<br>**Third-line treatment:** olanzapine, ziprasidone, carbamazepine, oxcarbazepine, asenapine, paliperidone<br>**Experiencing depressive symptoms**<br>**First-line treatment:** lamotrigine, lithium,[±] quetiapine<br>**Second-line treatment:** asenapine<br>**Comorbid ADHD**<br>**First-line treatment:** methylphenidate, mixed amphetamine salts<br>**Second-line treatment:** guanfacine<br>**Third-line treatment:** atomoxetine |
| Comorbid Anxiety in Unipolar Depression or Bipolar Disorder | |
| **No history of antidepressant-induced mania**<br>**First-line treatment:** citalopram, sertraline, escitalopram, fluvoxamine<br>**Second-line treatment:** clonazepam, gabapentin<br>**History of antidepressant-induced mania**<br>**First-line treatment:** clonazepam, gabapentin | |

[±]Especially if comorbid ADHD is present
[±±]Check EKG if dose is >600 mg
[±±±]Especially if there is a family history of lithium response

[1]Schneck C, Chang K, Singh M, DelBello M, et al: A pharmacologic algorithm for youth who are at high risk for bipolar disorder. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (November):796–805. From the University of Colorado School of Medicine, Aurora; and other institutions. **Funded by the NIMH; and the National Association for Research on Schizophrenia and Depression. Four of 5 study authors declared financial relationships with commercial sources.**

[2]Miklowitz D, et al: Early intervention for symptomatic youth at risk for bipolar disorder: a randomized trial of family-focused therapy. *Journal of the American Academy of Child and Adolescent Psychiatry* 2013;52:121–131.

***Common Drug Trade Names*: aripiprazole—*Abilify*; asenapine–*Saphris*; atomoxetine—*Strattera*; bupropion—*Wellbutrin*; carbamazepine—*Tegretol*; citalopram—*Celexa*; clonazepam—*Klonopin*; divalproex—*Depakene, Depakote*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; gabapentin—*Neurontin*; guanfacine—*Intuniv, Tenex*; lamotrigine—*Lamictal*; lurasidone—*Latuda*; methylphenidate—*Ritalin*; mixed amphetamine salts—*Adderall*; olanzapine—*Zyprexa*; oxcarbazepine—*Trileptal*; paliperidone—*Invega*; quetiapine—*Seroquel*; risperidone—*Risperdal*; sertraline—*Zoloft*; venlafaxine—*Effexor*; ziprasidone—*Geodon***

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**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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## Buspirone for GAD

In children and adolescents with generalized anxiety disorder, buspirone (*BuSpar*) is well tolerated, with a similar adverse-effect profile to adults, but there is insufficient evidence to support or refute its efficacy, according to a literature review and reanalysis of data.

***Background:*** Antidepressant treatment does not produce response in nearly 40% of youth with anxiety disorders. Medications with alternate mechanisms of action are commonly used in these patients despite limited or nonexistent safety, tolerability, and efficacy data in pediatric patients. Buspirone is approved for treatment of anxiety in adults, and case reports have suggested it may be effective in younger patients.

***Methods:*** A literature review was conducted to identify studies of pediatric buspirone use for anxiety. Data on pharmacokinetics, safety, tolerability, and efficacy were extracted from the studies and then re-evaluated.

***Results:*** Only 2 randomized trials in pediatric patients with GAD were found. Both were conducted nearly 2 decades ago, and the results were never published. Pharmacokinetic evaluations found a generally similar profile to adults. The efficacy trials, both multicenter U.S. studies, were similar in design, with a combined population of 558 patients, aged 6–17 years, with GAD. Participants received treatment for 6 weeks with placebo or either flexible-dose buspirone (15–60 mg/day) or buspirone in 2 fixed dosage ranges (15–30 mg/day or 45–60 mg/day). Change from baseline in the sum of the 4 anxiety items of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children was the primary efficacy outcome in both trials.

The reanalysis of data from the flexible-dose trial revealed a lack of statistically significant difference between buspirone and placebo, with an effect size* of 0.14. According to a Bayesian analysis, the studies were underpowered to detect significant differences. Adverse events in the 2 studies were minimal, and lightheadedness was the only event significantly elevated relative to placebo.

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***Discussion:*** Recently, failed and negative trials in pediatric psychiatry have been attributed to high placebo response rates. Other aspects of the FDA Modernization Act, which grants an additional 6 months of market exclusivity to drug manufacturers who investigate in children and adolescents agents already approved for use in adults, could have contributed additional biases toward inconclusive results. Furthermore, the outcome measure for the buspirone trials does not reflect the full range of symptoms or functional difficulties in young people with GAD. Because of these and other important limitations, the existing evidence base neither supports nor refutes the efficacy of buspirone for pediatric GAD; additional larger and more rigorous studies are needed.

Strawn J, Mills J, Cornwall G, Mossman S, et al: Buspirone in children and adolescents with anxiety: a review and Bayesian analysis of abandoned randomized controlled trials. *Journal of Child and Adolescent Psychopharmacology* 2018;28 (February):2–9. From the University of Cincinnati, OH; and other institutions. **Source of funding not stated. Two of 7 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

## Mania: Predicting Response to Olanzapine

Early improvement is the best predictor of eventual response and remission with olanzapine (*Zyprexa*), according to a clinical trial in adolescents with manic or mixed-episode bipolar disorder.[1] This finding strengthens the case for reliance on early improvement to inform the decision of whether to switch medication.

***Methods:*** This post-hoc analysis was conducted using data from a randomized, placebo-controlled trial of olanzapine in 161 adolescents, aged 13–17 years.[2] Participants had a diagnosis of DSM-IV-TR bipolar I disorder and were currently experiencing a manic or mixed episode, with a baseline Young Mania Rating Scale (YMRS) total score of ≥20. Those randomized to active treatment received flexible-dose olanzapine (2.5–20 mg/day) for 3 weeks. The primary efficacy outcome in the parent study was change from baseline to week 3 in the YMRS score. Early response was defined as a ≥25% reduction in YMRS score, ultimate response as a ≥50% reduction, and remission as a final score of ≤12 (standard definition) or ≤8 (stringent definition). For the present analysis, potential predictors of ultimate response and remission were evaluated.

***Results:*** Study participants had a mean age of 15 years and had illness onset a mean of 3 years previously. A total of 72 patients (69%) met criteria for early response to olanzapine. These early responders were more likely to have mixed episodes than early nonresponders, had higher baseline scores on the YMRS items for sleep and thought content, and received lower doses of olanzapine during double-blind treatment.

Early response was strongly predictive of ultimate response and remission. (See table.) Early responders also had greater average reductions in YMRS total score, as well as greater improvement on secondary outcome measures including the Clinical Global Impression Severity and Improvement scales and the Overt Aggression Scale.

**Early response vs nonresponse as predictor of ultimate treatment outcomes**

| Outcome | Early responders (n=72) | Early nonresponders (n=32) | Significance |
|---|---|---|---|
| **Ultimate response** | 44 (61%) | 7 (22%) | p<0.001 |
| **Standard remission (YMRS ≤12)** | 33 (46%) | 4 (12.5%) | p<0.001 |
| **Stringent remission (YMRS ≤8)** | 24 (33%) | 1 (3%) | p<0.001 |
| **Mean change in YMRS total score** | -56.4% | -29.8% | p<0.001 |

Statistical calculations identified an optimal cutoff point of a 35.5% reduction in YMRS score during week 1 as having the greatest accuracy in predicting ultimate response, with both a sensitivity and specificity* of about 70%. A cutoff of a 39% YMRS reduction at week 1 was the most accurate predictor of remission. In a multivariate analysis, early response was the strongest predictor of ultimate response; other significant predictors for individual outcomes included schizophrenia in a second-degree relative, fewer previous psychiatric hospitalizations, and male gender. Most adverse effects did not differ between early responders and nonresponders.

***Discussion:*** These observations suggest initial treatment of mania should be reevaluated in patients who do not show substantial improvement within the first week. A 35% decrease in symptom score appear to be an appropriate threshold to gauge early improvement.

[1]Xiao L, Ganocy S, Findling R, Chang K, et al: Baseline characteristics and early response at week 1 predict treatment outcome in adolescents with bipolar manic or mixed episode treated with olanzapine: results from a 3-week, randomized, placebo-controlled trial. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.16m10923. From Capital Medical University, Beijing, China; and other institutions. **Funded by Eli Lilly and Company. Six of 9 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Tohen M, et al: Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *American Journal of Psychiatry* 2007;164:1547–1556.

***See Reference Guide.**

## Predictors and Moderators of Depression Relapse

In an analysis of clinical-trial data, children and adolescents whose depression was successfully treated with fluoxetine (*Prozac*) had an increased risk of relapse if they had comorbid dysthymia at baseline and higher levels of residual symptoms after acute treatment.[1] Relapse rates were also higher in girls than in boys.

***Methods:*** This secondary analysis was based on a clinical trial of continuation therapy with fluoxetine.[2] Study participants, aged 7–18 years, had a ≥4-week history of major depressive disorder of at least moderate severity. Response was assessed after 12 weeks of treatment with open-label fluoxetine and was defined as a reduction of ≥50% in the Children's Depression Rating Scale–Revised (CDRS-R) score and a Clinical Global Impression–Improvement rating of much improved or better. Patients who met response criteria were randomly assigned to an additional 6 months of continued fluoxetine or a switch to placebo. Relapse was defined as a CDRS-R total score of ≥40. Potential predictors and mediators of relapse were chosen based on the findings of recent large-scale studies of depression treatment in young patients. Both predictors and moderators are present before treatment; predictors influence outcomes regardless of treatment type, while moderators affect the outcome differently depending on treatment.

***Results:*** Of 168 patients who received fluoxetine, 102 met response criteria and were randomly assigned to continued fluoxetine or placebo. Patients had a mean age of 11.5 years, and slightly more than half were boys. Relapse occurred during the 6-month extension period in 36 study participants and was less common with fluoxetine than with placebo (22% vs 48%; p=0.007).

No baseline demographic or illness characteristics were predictive of relapse. Relapse was predicted by comorbid dysthymia at baseline and by both child and parent perception of poor leadership in the family. Odds of relapsing were also increased in patients with higher depression scores or with residual sleep disturbance after acute treatment.

Gender was a moderator of relapse in fluoxetine-treated patients only, with a nearly 9-fold greater risk of relapse in girls than in boys who continued the drug. (See table, next page). Boys who received fluoxetine had a much lower risk of relapse than those who received placebo.

A higher average CDRS-R score at randomization predicted a higher likelihood of relapse in patients who received fluoxetine, but not placebo. Among patients with no residual insomnia at week 12, the odds of relapsing were significantly lower with fluoxetine than placebo. Comorbid dysthymia, family leadership, and residual irritability were not moderators of the relationship between treatment and relapse prevention.

**Predictors and moderators of treatment relapse in multiple regression models**

| Predictors | Odds ratio* | Significance |
|---|---|---|
| Comorbid dysthymia | 2.88 | p=0.03 |
| Perception of poor family leadership<br>Child score<br>Parent score | <br>1.39<br>1.24 | <br>p=0.006<br>p=0.05 |
| Week 12 depression severity (CDRS-R) | 1.21 | p=0.003 |
| Week 12 residual insomnia | 6.74 | p=0.006 |
| **Moderators in fluoxetine-treated patients** | **Odds ratio** | **Significance** |
| Female vs male | 8.86 | p=0.007 |
| Baseline CDRS-R total score± | 1.14 | p=0.03 |
| Anxiety score at randomization | 0.19 | p=0.002 |
| No residual insomnia | 0.12 | p=0.006 |

Odds ratios are adjusted for treatment (fluoxetine vs placebo), age, gender, and CDRS-R at start of continuation treatment.
±Odds of relapse were multiplied by 1.14 (i.e., 14% higher) for every 1-unit increase in the CDRS-R score.

***Discussion:*** Current guidelines recommend continuing medication for 6–9 months after response to an antidepressant. Nevertheless, relapse rates are still high. The present study has identified some factors that could help identify patients who would benefit from additional psychoeducation and treatment tailored to their specific risk factors. The results of the moderator analysis are difficult to interpret because moderator analyses generally require a larger sample size, and the findings regarding placebo are not relevant to real-world practice.

[1]Kennard B, Mayes T, Chahal Z, Nakonezny P, et al: Predictors and moderators of relapse in children and adolescents with major depressive disorder. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.15m10330. From the University of Texas Southwestern Medical Center and Children's Medical Center, Dallas. **Funded by the NIMH. One of 6 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Emslie G, et al: Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. *American Journal of Psychiatry* 2008;165:459–467. See *Child & Adolescent Psychiatry Alerts* 2008;10 (April):21.

***See Reference Guide.**

## Gene-Targeted Therapy in ADHD

Fasoracetam, a metabotropic glutamate receptor (mGluR) activator, was well tolerated and showed preliminary evidence of efficacy in adolescents with ADHD who had variants in mGluR network genes.

***Background:*** Copy number variants (CNVs) in the mGluR gene network occur in an estimated 11% of children with ADHD, about 10-times the frequency in unaffected children. Fasoracetam is an investigational drug that has undergone clinical trials for vascular dementia and has been shown to reverse induced memory and learning deficits in animal models.

***Methods:*** The present phase I trial was conducted in 30 patients, aged 12–17 years, with a diagnosis of ADHD who had been screened for mGluR mutations in a large-scale genomic study. After a washout of previous medications, participants underwent 24-hour pharmacokinetic testing. Afterward, all participants received single-blind placebo for 1 week, followed by

fasoracetam in weekly escalating dosages of 50, 100, 200, and 400 mg b.i.d. Efficacy was measured using the Clinical Global Impression (CGI) Improvement and Severity scales,* the Vanderbilt Parent Scale, and the parental Behavior Rating Inventory of Executive Function (BRIEF).

***Results:*** Patients showed clinical improvement on all 4 efficacy measures during each week of active treatment. The strongest improvements were in the CGI-I score, which decreased from a mean of 3.8 during the placebo week to 2.3 during the final week of treatment. The mean CGI-S score decreased from 4.9 to 3.93. Significant improvement did not occur until the second active treatment week, which suggests a minimum dosage of 100 mg b.i.d. may be required to observe a benefit. Improvements in the Vanderbilt and BRIEF measurements were less pronounced than those in the CGI scales.

In an additional analysis, patients were stratified into 3 tiers according to specific mGluR variants. The 2 highest-risk tiers had significantly larger CGI-I and CGI-S responses than the group with less severe mutations. Actigraphy monitoring, performed throughout the study, showed that adolescents had a net reduction of moderate-to-high intensity and repetitive movements between the placebo week and the highest-dosage week. Adverse events were mild and occurred at similar rates during placebo and drug administration.

***Discussion:*** Although preliminary, these study results support the continued investigation of fasoracetam as a treatment for ADHD. They also highlight the value of genetic prioritization and targeted therapy in ADHD.

Elia J, Ungal G, Kao C, Ambrosini A, et al: Fasoracetam in adolescents with ADHD and glutamatergic gene network variants disrupting mGluR neurotransmitter signaling. *Nature Communications* 2018; doi 10.1038/s41467-017-02244-2. From Nemours/Alfred I. du Pont Hospital for Children, Wilmington, DE; and other institutions. **Funded by neuroFix Therapeutics Inc. One of 24 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

## Mixed-Release Amphetamine

The newly-approved triple-bead mixed amphetamine salts SHP465 (*Mydayis*) was effective and well tolerated in a clinical trial in children and adolescents. The new formulation contains 3 types of drug-releasing beads, providing immediate and delayed release at pH values of 5.5 and 7.

***Methods:*** Study participants, recruited from 36 U.S. sites, were aged 6–17 years and had a primary diagnosis of DSM-IV-TR ADHD, with a baseline ADHD Rating Scale-IV (ADHD-RS-IV) score of ≥28. After a washout of previous medications, patients were randomly assigned to receive double-blind treatment with 12.5 mg SHP465 or placebo, taken once daily at 7AM. At the end of the first study week, the dose was increased to 25 mg based on response and tolerability. The primary efficacy outcome, assessed after 4 weeks, was change from baseline in the ADHD-RS-IV total score. The 4-week score on the Clinical Global Impression–Improvement* scale was the key secondary endpoint.

***Results:*** Of 264 enrolled patients, about 40% were aged ≤12 years, and 234 completed the study. The most frequent reasons for withdrawal were adverse events (11 patients receiving SHP465 and 3 receiving placebo) and lack of efficacy (1 with SHP465, 4 with placebo). The optimal daily dose of SHP465 was 25 mg in 72% of patients and 12.5 mg in 24%.

At baseline, the mean total ADHD-RS-IV scores were 39 and 40 in the SHP465 and placebo groups, respectively. At the 4-week assessment, scores were reduced by 21 points with SHP465, compared with 11 points with placebo (effect size,* 0.80; $p<0.001$). Scores on both

the hyperactivity/impulsivity and inattentiveness subscales decreased to a significantly larger extent with SHP465 than placebo ($p<0.001$ for both). The mean CGI-I score at week 4 was 3 for placebo and 2.2 for SHP465 (effect size, 0.65; $p<0.001$).

The most frequently reported adverse events with SHP465 were decreased appetite and insomnia. Of the adverse events that led to study discontinuation, 9 were related to the study drug. All were of mild or moderate severity and resolved with treatment discontinuation.

***Discussion:*** Previously published studies have shown that SHP465 is safe and efficacious in adults. This is the first published phase III study in children and adolescents; the agent is approved for use in patients aged ≥13 years. Although efficacy cannot be compared directly, the effects of SHP465 appear similar to other long-acting stimulants. The adverse-effect profile is also consistent with other long-acting amphetamines.

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

Brams M, Childress A, Greenbaum M, Yu M, et al: SHP465 mixed amphetamine salts in the treatment of attention-deficit/hyperactivity disorder in children and adolescents: results of a randomized, double-blind placebo-controlled study. *Journal of Child and Adolescent Psychopharmacology* 2018;28 (January):19–28. From Baylor College of Medicine, Houston, TX; and other institutions including Shire, Lexington, MA. **Funded by Shire Development, LLC. All study authors disclosed financial relationships with commercial sources including Shire.**

***See Reference Guide.**

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

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

**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

**Odds Ratio:** A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**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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## Antidepressants in Anxiety

In children and adolescents with anxiety disorders, antidepressant-related improvements occur quickly and SSRIs are associated with earlier and larger improvement than SNRIs, according to the results of a meta-analysis.

***Background:*** SSRIs and SNRIs have both been recommended as first-line treatment for pediatric anxiety disorders. However, duloxetine is the only FDA-approved antidepressant for this indication, and it is unknown whether SSRIs are superior to SNRIs. The present meta-analysis was conducted to evaluate the trajectory of response to antidepressants in pediatric anxiety disorders and to compare the effects of drug class and dose.

***Methods:*** Studies were included if they were prospective, randomized, parallel-group, placebo-controlled trials that evaluated the efficacy of SSRIs or SNRIs in social, generalized, and/or separation anxiety disorder in patients aged ≤18 years. For inclusion, studies were required to use a standardized rating scale to measure anxiety symptoms. The primary outcome of the analysis was change from baseline on a standardized measure of anxiety for the active medication in comparison with placebo. Dose comparisons were based on fluoxetine equivalents of the labeled therapeutic range of each drug. Atomoxetine was included in the analysis because of its potent norepinephrine reuptake blockade and serotonin transporter inhibition.

***Results:*** The comprehensive literature search identified 9 studies conducted in 1805 patients, evaluating 7 different drugs: 4 SSRIs (i.e., fluoxetine, fluvoxamine, paroxetine, and sertraline) and 3 SNRIs (i.e., atomoxetine, duloxetine, and venlafaxine). The median study duration was 10 weeks. The Pediatric Anxiety Rating Scale was the outcome measure in all but 2 studies.

Overall, statistically significant differences between drug and placebo appeared at week 2 ($p=0.005$) and reached a clinically significant effect size* of 0.44 by week 6 ($p=0.001$). Both SSRIs and SNRIs were associated with statistically significant improvement, relative to placebo, at treatment week 2 and remained statistically superior to placebo up to week 12. SSRIs were superior to SNRIs beginning at week 2 ($p=0.026$) and continuing to week 12 ($p<0.03$ for all

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2-week intervals). The results were essentially unchanged in a sensitivity analysis that excluded data from the atomoxetine trial. Industry-funded and government-funded studies had generally similar results. Low doses of SSRIs (<1.5 fluoxetine equivalents per day) were no less effective than higher doses overall, but high doses were associated with an earlier response.

***Discussion:*** These results suggest that SSRIs may be more effective than SNRIs against pediatric anxiety. It is possible that SSRIs could be superior because the serotonin system matures earlier than the noradrenergic system and may be a more available treatment target. In addition, SNRIs have class-specific tolerability concerns, including suicidality with venlafaxine. The study findings regarding dosage raise questions regarding the long-held belief that antidepressants should be titrated.

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

Strawn J, Mills J, Sauley B, Welge J: The impact of antidepressant dose and class on treatment response in pediatric anxiety disorders: a meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry* 2018;57 (April): 235–244. From the University of Cincinnati College of Medicine; and other institutions, OH. F**unded by the NIMH. Two of 4 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

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

***See Reference Guide.**

## Predictors of Suicide After Self-Harm

In adolescents and young adults, risk of suicide was markedly elevated in the year following treatment for an episode of nonsuicidal self-injury. Risk was particularly high in males, American Indian and Alaskan Natives, and individuals who had used a violent method of self-harm.

***Methods:*** The study was conducted to investigate the relative strengths of known risk factors for suicide, such as demographics, psychiatric disorders, and methods of self-harm, and to determine whether risk profiles differed between adolescents and young adults. Data were extracted from Medicaid records covering 45 states between 2001 and 2007. The cohort included patients, aged 12–24 years, with a clinical diagnosis of deliberate self-harm, who were followed for up to 1 year after receiving treatment for the injury. Study outcomes were repeated self-harm and death from suicide.

***Results:*** A total of 32,395 initial nonfatal self-harm events were observed. About 17% of the patients had a second episode of self-harm during the follow-up year, with the maximum risk occurring in the first few days after the initial event. Adjusted risks of a repeat self-harm event were higher in females (hazard ratio* [HR], 1.33) and in American Indian and Alaskan Natives (HR, 1.18). A recent clinical diagnosis of ADHD was not associated with risk of repeated self-harm, but all other psychiatric diagnoses were, with particularly high risk in patients with personality (HR, 1.36) or anxiety disorders (HR, 1.24). Risk profiles did not differ substantially between adolescents (aged ≤17 years) and young adults.

During the 1-year follow-up, there were 48 completed suicides, 23 in adolescents and 25 in young adults. Mortality from suicide was nearly 27 times higher in this cohort than in the general U.S. population, matched for age, gender, and race and/or ethnicity. Adolescents with a history of self-injury were 46 times more likely than their peers in the general population to commit suicide, and young adults were 19 times more likely. After controlling for age and gender, the risk of suicide following self-harm was elevated in American Indian and Alaskan Natives (HR, 5.6), and individuals who had used a violent method (HR, 13.6), such as firearms (HR, 33.5), for their index episode of self-injury. Suicide risk was about 4-times higher in boys than in girls; however, they were significantly more likely to have used a

violent method during their initial self-harm event. Suicide rates were relatively low in African American and Hispanic individuals compared with whites, but these differences were not statistically significant.

***Discussion:*** Nonfatal self-harm is strongly associated with both repeated nonfatal self-harm and suicide in the subsequent year, indicating the need for careful follow-up for all patients who self-harm. The present results suggest suicide prevention efforts may be especially necessary in males and those whose initial episode of self-harm was violent.

Olfson M, Wall M, Wang S, Crystal S, et al: Suicide after deliberate self-harm in adolescents and young adults. *Pediatrics* 2018; doi 10.1542/peds.2017-3517. From Columbia University, New York, NY; and other institutions. **Funded by the Agency for Healthcare Research and Quality. The authors declared no competing interests.**

***See Reference Guide.**

## Early Irritability and Suicide Risk

Irritability in childhood was predictive of increased risk of suicidal behaviors in adolescence in a population-based cohort study that used an innovative method of developmental-trajectory modeling.

***Methods:*** The study cohort consisted of a representative sample of children born in the Canadian province of Quebec in 1997 and 1998 and followed through adolescence. At ages 6, 7, 8, 10, and 12 years, children were assessed by their teachers using the Behavior Questionnaire, a composite of items from several different standardized instruments. The questionnaire rated depressive/anxious mood with 9 items and irritability with 4 items. Serious suicidal ideation and suicide attempts were assessed by directly questioning study participants when they were aged 13, 15, and 17 years. Evaluation of developmental trajectories of irritability and depressive/anxious mood from ages 6–12 years resulted in 5 specific profiles: no irritability and low depressive/anxious mood; low irritability and low depressive/anxious mood; moderate irritability and low depressive/anxious mood; moderate declining irritability and high depressive/anxious mood; and high irritability and depressive/anxious mood. The 2 profiles with the lowest symptom levels and risk of adolescent suicidal behavior were merged and used as the reference group for estimation of odds ratios* and the number needed to be exposed* (NNE) for the other groups.

***Results:*** The study included 1430 children who were followed through adolescence. More than half belonged to the 2 profiles with no or low irritability and low depressive/anxious mood. Members of the profile with the highest symptom levels were more likely than others to be male, from a socioeconomically advantaged family, and to be raised by a depressive and/or hostile-reactive mother.

**Risk of suicidal behavior (serious ideation or attempt) during adolescence by childhood profile of irritability and depressed/anxious mood**

| Profile | | Subjects | Odds ratio for suicidal behavior† | NNE |
|---|---|---|---|---|
| Irritability | Depressed/anxious mood | | | |
| Moderate | Low | n=353 (25%) | 1.51 | 48 |
| Moderate declining | High | n=94 (7%) | 0.96 | -320 |
| High | High | n=152 (11%) | 2.22 | 18 |

†Adjusted for gender, socioeconomic status, and age

Overall rates of suicidal behavior ranged from 10.6 % (low irritability, high depressive/anxious mood) to 16.4% (high on both traits). In an adjusted analysis, the odds of suicidal ideation and attempts were significantly elevated in adolescents who, as children, had high levels of irritability. The effect was particularly pronounced in girls. Moderate irritability plus low anxiety/depression was also associated with a more modest increase in suicidal behavior, with a slightly larger impact in boys.

***Discussion:*** Children with high irritability and depressive/anxious mood and, to a lesser extent, those with moderate irritability appear to be at greater risk for suicidal behavior during adolescence compared with children with low symptom levels. However, in part because the scales used to assess symptoms in childhood were administered by teachers and were not clinical diagnostic instruments, the results must be viewed as preliminary and require replication before being used to create clinical screening recommendations.

Orri M, Galera C, Turecki G, Forte A, et al: Association of childhood irritability and depressive/anxious mood profiles with adolescent suicidal ideation and attempts. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.0174. From the Institut National de la Sante et de la Recherche Medicale, Bordeaux, France; and other institutions. **Funded by the Quebec Government; and other sources. Five of 9 study authors disclosed potentially relevant relationships with noncommercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

## OCD: Longitudinal Comorbidity

According to the results of a community-based cohort study, adolescents and young adults with obsessive-compulsive disorder are at increased risk for onset of other psychiatric disorders, particularly bipolar disorder and bulimia.

***Background:*** There are several plausible mechanisms by which OCD could lead to subsequent mental-health disorders. Affective disorders could result from the demoralizing effects of obsessions and compulsions. Anxiety symptoms, already present in OCD, could progress into a clinical anxiety disorder, such as panic disorder or social phobia. Structural brain alterations in OCD could leave adolescents' brains more vulnerable to development of other disorders. Social discomfort because of obsessions and compulsions could put individuals with OCD at risk for social phobia. Cross-sectional relationships of OCD with other disorders have been observed in previous research. However, few studies have used longitudinal designs to evaluate the temporal relationship between OCD and subsequent development of other psychiatric disorders.

***Methods:*** Data were collected from the Early Developmental Stages of Psychopathology study, a 10-year, prospective study from Munich, Germany. The study enrolled individuals who were aged 14–24 years at the 1995 baseline. Participants were assessed at entry and in 3 subsequent waves, with the last concluding 10.6 years after baseline. Mental health was measured using the Munich-Composite International-Diagnostic-Interview, a 2–3-hour face-to-face clinical interview assessing the presence of DSM-IV disorders. In addition to estimating the temporal relationship of OCD to other disorders, the investigators also estimated the attributable fraction and the population attributable fraction—i.e., the proportion of subsequent disorders that would not have occurred in the absence of OCD in persons identified with OCD and in the general population, respectively. These can provide a rough estimate of the potential impact of interventions to prevent OCD on the development of subsequent disorders.

***Results:*** The analysis was based on 3021 study participants. At enrollment, 20 individuals (0.7%) met diagnostic criteria for OCD. By the end of follow-up, 55 persons (1.8%) met criteria for OCD. Nearly all patients with OCD had ≥1 comorbid psychiatric disorder.

After adjustment for age, gender, and other disorders occurring prior to OCD diagnosis, presence of OCD was significantly associated with later development of bipolar disorder, bulimia

nervosa, dysthymia, social phobia, and generalized anxiety disorder. (See table.) There was no association between OCD and later development of depression or substance use disorders. The highest attributable fractions in patients with OCD (>80%) were observed for bipolar disorder and bulimia, and attributable fractions were >65% for other disorders. At the population level, between 1.5% and 7.7% of the incidence of other disorders was attributable to prior OCD, assuming a causal relationship.

**Association of OCD with later onset of other mental disorders**

| Disorder | Hazard ratio* |
|---|---|
| Bipolar disorder | 6.9 |
| Bulimia nervosa | 6.8 |
| Dysthymia | 4.4 |
| Generalized anxiety disorder | 3.4 |
| Social phobia | 2.9 |

***Discussion:*** The present data suggest that OCD can be conceptualized as a risk factor for other disorders. The large attributable fractions suggest that early treatment efforts in OCD could reduce the onset of many secondary mental disorders. Population attributable fractions were relatively low because of the low prevalence of OCD in the general population.

Hofer P, Wahl K, Meyer A, Miche M, et al: Obsessive-compulsive disorder and the risk of subsequent mental disorders: a community study of adolescents and young adults. *Depression and Anxiety* 2018; doi 10.1002/da.22733. From the University of Basel, Switzerland; and other institutions. **Funded by the German Federal Ministry of Education and Research. The authors did not include disclosure of potential conflicts of interest.**

***See Reference Guide.**

## ADHD-Related Time Management Deficits

In a randomized trial, a multimodal intervention improved time management skills in children and adolescents with ADHD.

***Background:*** Time-related difficulties that interfere with daily routines, homework, school work, and social relations have been recognized in children with ADHD. However, the primary treatments for ADHD do not specifically address these time-related problems.

***Methods:*** Study participants were families of children, aged 9–15 years, receiving treatment for ADHD. Despite pharmacotherapy, participating children had difficulties in daily time management, reported by parents on a structured questionnaire. The multimodal study intervention had 3 components: advocacy, compensation, and remediation. The advocacy component was delivered to all families and comprised a session with an occupational therapist to identify and prioritize the child's time management issues, followed by a 6-hour manualized, group education session for the parents and the child's coach. The lectures focused on deficits in time processing ability in ADHD, how to compensate, and how to support children with these deficiencies. In addition, the randomly selected intervention group received the compensation and remediation components. Compensation consisted of 3 or 4 sessions with both the parents and child, focusing on finding strategies to compensate for deficits, structuring the environment, and prescribing time-assisted devices such as alarms, schedules, or pictures. In the remediation component, the child performed 10 tasks from a series of up to 14 challenging time-skill training tasks of increasing complexity, with the support of a coach. The primary study outcome measures were the Kit for assessing time-processing ability (KaTid), the Time-Parent scale questionnaire, and the Time-Self-rating questionnaire. The interventions took place over 12 weeks, and outcomes were assessed after an additional 12 weeks of usual ADHD care.

***Results:*** A total of 46 families were randomized, of which 38 completed the program and were evaluated at 24 weeks. Overall, time-processing ability improved in all children, but to a significantly greater degree in the group receiving the multimodal interventions (see table, next page), but effect sizes* were small. The KaTid time management subscale and self-reported daily time management improved comparably in the 2 groups.

| Change from baseline in time-processing ability and daily time management in children receiving a multimodal intervention vs controls | | |
|---|---|---|
| | **Effect size** | **Significance** |
| **Time-processing ability (KaTid)** | | |
| Total score | 0.38 | p=0.019 |
| Time perception subscale | 0.29 | p=0.046 |
| Orientation to time subscale | 0.42 | p=0.01 |
| Time management subscale | 0.03 | p=NS |
| **Daily time management** | | |
| Time—Parent scale | 1.0 | p=0.011 |
| Time—Self-report scale | -0.37 | p=NS |

***Discussion:*** The 3 subscales of time-processing ability on the KaTid measure developmentally different ability levels, and the challenging tasks were also geared toward these levels. The children tended to complete lower-level challenges, related to time perception and time orientation, but may have not been sufficiently developmentally advanced to benefit from challenges to improve time management, the highest level. It is also not surprising that parents rated time management more highly than children, since the intervention may have made children more aware of their limitations.

Wennberg B, Janeslatt G, Kjellberg A, Gustafsson P: Effectiveness of time-related interventions in children with ADHD aged 9–15 years: a randomized controlled study. *European Child and Adolescent Psychiatry* 2018; doi 10.1007/s00787-017-1052-5. From Linköping University, Sweden; and other institutions. **Funded by the Medical Research Council of Southern Sweden; and other sources. The authors declared no competing interests.**

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**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

**Number Needed to Be Exposed:** A measure of how many patients need to have a specific risk factor to cause the outcome of interest in 1 patient. Lower NNE 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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**Change Coming . . . See back page for details.**

## Saffron Extract for Anxiety and Depression

In a manufacturer-sponsored controlled trial, a standardized saffron extract (*affron*) reduced self-reported anxiety and depression symptoms in adolescents.

***Methods:*** Study participants, aged 12–16 years, with anxiety or depression were recruited from the community through social and conventional media. Symptoms were assessed using the Revised Child Anxiety and Depression Scale (RCADS), and adolescents were included in the study if they had mild-to-moderate symptoms (i.e., scores >60th population-standardized percentile and below the 90th percentile on the total RCADS or on a subscale). Patients engaging in self-harm or with suicidal thoughts were excluded. Study participants were randomly assigned to receive a twice-daily standardized saffron extract in tablet form or placebo for 8 weeks. The primary outcome was change from baseline on the self-report RCADS. Parent-reported symptom scores were a secondary outcome.

***Results:*** The 80 study participants had a mean age of 14 years, and about one-third were male. Of those enrolled, 12 patients withdrew from the study, most often because of refusal to take the tablets (n=5), worsening mental health (n=2), or commencement of other treatment (n=2). Discontinuation rates did not differ between treatment groups.

Saffron extract produced a larger reduction than placebo in youth-reported RCADS total anxiety scores and total internalizing scores, with effect sizes* of 0.58 and 0.61, respectively. Adolescents who received saffron demonstrated significantly larger improvements than the placebo group on several of the RCADS subscales including depression (p=0.016; effect size, 0.60), separation anxiety (p=0.003; effect size, 0.62), and social phobia (p=0.023; effect size, 0.58). Differences in generalized anxiety improvement also favored saffron but did not reach statistical significance (p=0.067; effect size, 0.44). Effect sizes were in the small-to-medium range. Parents of adolescents who received saffron also reported numerically larger improvements in their children's symptoms than those who received placebo, but these differences were smaller and not statistically significant.

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Participants who received saffron had a 33% mean reduction in total internalizing symptoms, compared with a 17% reduction with placebo (p=0.029). Rates of response, defined as a ≥50% reduction in total internalizing symptoms, were 37% with saffron and 11% with placebo (odds ratio,* 4.81; p=0.014).

***Discussion:*** The beneficial effects of saffron in the present study were smaller than those previously reported in the adult literature. However, the adult studies were conducted in patients with major depressive disorder, possibly accounting for some of the difference in effect sizes. The mechanisms of action of saffron are uncertain but may include antioxidant and anti-inflammatory effects, reduction of plasma corticosterone, and increases in brain concentrations of dopamine (without affecting serotonin or norepinephrine). Studies longer than 8–12 weeks in duration have not been conducted in adults or young patients, leaving the long-term efficacy of saffron extract undetermined.

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

Lopresti A, Drummond P, Inarejos-Garcia A, Prodanov M: affron®, a standardised extract from saffron (Crocus sativus L.) for the treatment of youth anxiety and depressive symptoms: a randomised, double-blind, placebo-controlled study. *Journal of Affective Disorders* 2018; doi 10.1016/j.jad.2018.02.070. From Murdoch University, Perth, Australia; and other institutions. **Funded by Pharmactive Biotech Products SL. The authors did not include disclosure of potential conflicts of interest.**

***See Reference Guide.**

## Marijuana Legalization and Adolescent Health

Survey data suggest that Colorado's legalization of medical marijuana in 2009, followed by recreational use in 2014, was not accompanied by increased use of the drug by adolescents. However, the number of marijuana-related emergency and urgent-care visits to a Colorado pediatric hospital increased nearly 5-fold in subsequent years.

***Methods:*** To assess the effect of legalization on one facet of adolescent health, the investigators examined data from admissions to the emergency and urgent-care facilities of a tertiary-care children's hospital system in the Denver metropolitan area. Data were collected from visits between 2005 and 2015 by patients aged 13–20 years with a discharge diagnosis of marijuana/cannabis use or with a positive toxicology screen for tetrahydrocannabinol (THC). Urine drug screens were mandatory for patients admitted for behavioral health disorders.

***Results:*** A total of 4202 marijuana-related visits occurred in patients with a mean age of 16 years (54% male) during the study years. The annual total increased steadily over the years, from 161 in 2005 to 777 in 2015. The number of behavioral health evaluations, which were provided for 67% of patients, also showed a steady increase from 84 in 2005 to 500 in 2015. The majority of patients received a diagnosis of cannabis use/abuse/misuse (62%) or substance abuse (33%). Comorbid psychiatric diagnoses were also common and included depression (39%), mood disorder (22%), conduct disorder (13%), anxiety/panic disorder (13%), ADHD (12%), bipolar disorder (6%), schizophrenia (5%), and "other" (31%).

Rates of marijuana-related visits, relative to all emergency/urgent care visits, were compared for 2009 and 2015, the first full years of medical and recreational marijuana legalization, respectively. The frequency increased from 1.8 per 1000 visits in 2009 to 4.9 per 1000 in 2015. Marijuana-related behavioral health consultations increased from 1.2 per 1000 visits in 2009 to 3.2 per 1000 visits in 2015.

***Discussion:*** Although there has been an increase in the frequency of urine drug screens overall, this does not fully account for the increase in cannabis-related visits. These data should prompt concern now that more than half of states have legalized at least some type

of marijuana use, in part because adolescents' risk perception of marijuana may have decreased, even if data do not consistently show an increase in actual use.

Wang G, Davies S, Halmo L, Sass A, et al: Impact of marijuana legalization in Colorado on adolescent emergency and urgent care visits. *Journal of Adolescent Health* 2018; doi 10.1016/j.jadohealth.2017.12.010. From the University of Colorado Anschutz Medical Campus; and Children's Hospital Colorado, Aurora, CO. **This research was conducted without specific funding. One of 5 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

## Treating Anxiety in Emerging Adulthood

The period of emerging adulthood can be complicated by the presence of anxiety disorders, in part because the developmental tasks of young adulthood are dependent on abilities, such as emotional regulation and social skills, which are often deficient in persons with anxiety or other psychiatric disorders. A newly developed cognitive-behavioral treatment program, the Launching Emerging Adults Program (LEAP), has been designed specifically for young adults with anxiety disorders and their families.

Emerging adulthood spans the years of age 18 to 25, approximately. Developmental milestones during this period usually include growth of self-identity, financial independence from parents, management of personal self-care, completion of education, and establishment of long-term relationships. Anxiety disorders are highly prevalent during these years, affecting from 12% to >25% of young adults in different cross-sectional studies. The transition to early adulthood is associated with a dramatic increase in the prevalence of anxiety disorders, most often as an extension of anxiety in childhood and adolescence. Cognitive behavioral therapy (CBT) is a well-supported treatment for anxiety disorders in children and adolescents. However, recent research suggests the effects of CBT are less robust in adolescence than in childhood, and its effects in these age groups may not be lasting.

The LEAP model of CBT was designed specifically for emerging young adults with anxiety and their families. LEAP targets individual factors that maintain anxiety and delays or deficits in life skills. The therapy also addresses parental behaviors that often interfere with the developmental tasks of young adulthood. The schedule includes both individual and family sessions plus group-based exposure sessions with peers. The program can be adapted flexibly, allowing for more intensive family work for low-functioning patients who live at home and are not employed or in school, or for little or no family involvement if the patient is living independently. The therapy is organized into 4 stages, with a flexible total of about 22 sessions.

**Phase 1.** The first 4 sessions heavily involve the family and focus on psychoeducation and identifying the patient's current level of function. In these sessions, the roles of avoidance and parent involvement in maintaining anxiety are addressed. Both patients and parents are provided with an instrument to track response to anxiety-provoking situations. This phase also includes goal setting and creation of a hierarchy of anxiety-provoking situations.

**Phase 2.** In sessions 5–10, responsibility for treatment and clinical focus are shifted to the patient. With less family involvement, the patient is taught cognitive restructuring and problem-solving skills. Role playing and behavioral experiments are incorporated to challenge anxiety-related negative predictions. Skill deficits and emotion dysregulation can be addressed using assertiveness and social-skills training, and patients are taught general affect regulation, relaxation, self-soothing, and problem solving. Communication skills and family problem-solving strategies are incorporated in the final session of this phase, attended by patients and parents, to facilitate independent functioning.

**Phase 3.** The third stage includes 2 types of peer-group experiences: group-based exposure to challenging situations, and optional "adulting" groups designed to help low-functioning

patients. Group exposures are offered at beginner, intermediate, and advanced levels and are designed to reduce avoidance of challenging situations and to improve coping skills. Patients test new skills, practice problem solving, and give and receive peer support. The "adulting" group is an optional short-term intensive program that meets several days per week for 2–3 weeks. It is intended to increase confidence and competence in completion of daily adult responsibilities and habits.

**Phase 4.** The final phase is aimed at solidifying gains, transitioning to the adult role, and preventing relapse. In the final patient–parent session, behavioral contracts are created to clearly define the responsibilities of each family member and to set goals for role transitions. The program concludes with several sessions promoting continued anxiety management and information on how to access posttreatment support.

In contrast to many existing anxiety therapies, LEAP directly addresses the patient's functional status and family framework while providing skill-building and exposure. Although the present report does not address efficacy of the program, testing of the model is ongoing along with development of potential uses of virtual reality environments to enhance contextual cues.

Hoffman L, Guerry J, Albano A: Launching Anxious Young Adults: a specialized cognitive-behavioral intervention for transitional aged youth. *Current Psychiatry Reports* 2018: doi 10.1007/s11920–018–0888–9. From Columbia University Medical Center, New York, NY; and other institutions. **Source of funding not stated. One study author disclosed a potentially relevant financial relationship; the remaining 2 authors declared no competing interests.**

## Pediatric Asenapine

Asenapine (*Saphris*) is a novel antipsychotic, approved in the U.S. as monotherapy for bipolar I disorder in children and adolescents aged 10–17 years. Approval was based on a single, 3-week, randomized, placebo-controlled trial. A 50-week open-label extension study provided additional safety and efficacy data. The manufacturer of asenapine also sought regulatory approval for treatment of pediatric schizophrenia. Drug effects did not differ significantly from placebo in the acute trial, and approval was not granted; however, an extension trial provided additional safety data. The drug was well tolerated in acute and long-term studies for both indications. Serious adverse events were generally related to worsening of the underlying psychiatric disorder. The most common treatment-emergent adverse events were somnolence, sedation, and oral symptoms. In the extension studies, weight gain was reported as an adverse event in 18% of study patients with bipolar disorder and about 14% of those with schizophrenia. Suicidal ideation was reported in patients with both bipolar disorder and schizophrenia, mostly limited to those who had a history of ideation. Extrapyramidal symptoms affected ≥5% of patients with both disorders and were generally mild or moderate.

Asenapine shares the dopamine $D_2$ and serotonin 5-$HT_{2a}$ receptor affinity of other second-generation antipsychotics, but also has a complex profile of activity at other receptors. It has high antagonist activity for multiple other dopamine and serotonergic receptors and for adrenergic and histamine receptors, moderate antagonist activity at the histamine $H_2$ receptor, and no apparent affinity for muscarinic receptors. These properties predict a low likelihood of anticholinergic effects but may cause sedation, weight gain, and cardiovascular effects. Asenapine is only available as a sublingual tablet, with 3 dose strengths. It must be dissolved under the tongue; bioavailability is markedly reduced if the tablet is swallowed. Pharmacokinetics are similar to those in adults, with a time to peak concentration of 1–2 hours and a time to steady state of about a week. Children and adolescents can take the recommended adult doses, but a short up-titration is recommended in pediatric patients to avoid dystonia and initial sensitivity. Eating and drinking should be avoided for 10 minutes after asenapine administration to prevent interference with mucosal absorption. In addition, consuming a high-fat meal immediately prior to sublingual asenapine administration can reduce drug exposure by as

much as 20%. Mouth and/or throat numbness or tingling may occur immediately after asenapine administration, but these sensations typically resolve within 1 hour. Somnolence and sedation may be treatment-limiting in some young patients.

Stepanova E, Grant B, Findling R: Asenapine treatment in pediatric patients with bipolar I disorder or schizophrenia: a review. *Pediatric Drugs* 2018;20 (April):121–134. From Johns Hopkins University; and other institutions, Baltimore, MD. **Funded by Allergan. Two of the 3 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

## Aripiprazole vs Quetiapine: QT Effects

In a head-to-head, randomized comparison study, extended-release quetiapine was associated with small but statistically significant increases in the QTc interval in children and adolescents with first-episode psychosis while aripiprazole was not. The quetiapine-associated changes were small and not likely to be clinically significant but they do indicate a need for caution in patients with cardiac risk factors.

***Methods:*** This analysis was part of a larger trial comparing the safety and efficacy of quetiapine and aripiprazole in patients aged 12–17 years with first-episode schizophrenia, psychotic disorders, mania or depression with psychotic symptoms, or related disorders. Participants were antipsychotic-naïve or had limited prior exposure to the drugs. After random assignment, quetiapine and aripiprazole were titrated using a standardized schedule to target dosages of 600 mg/day extended-release quetiapine and 20 mg/day aripiprazole; maximum permitted dosages were 800 mg/day and 30 mg/day, respectively. Patients received treatment for 12 weeks. ECGs were obtained before starting study medication and at weeks 4 and 12 of treatment. For this analysis, the primary outcome measure was the corrected QT interval (QTc). QT variability or dispersion (QTd) was measured as the difference between the maximum and minimum QTc intervals in 2 or 3 consecutive complexes in 5 or 6 leads.

***Results:*** A total of 93 patients were included in the comparison of QTc and 49 in the analysis of QTd. Baseline values for these measurements did not differ between patients with or without prior exposure to antipsychotics. In patients who received quetiapine, the mean change in the QTc from baseline to 12 weeks was 6.8 ms (p=0.025). The increase was evident at the 4-week evaluation and did not increase further after that time. The QTc did not change significantly in aripiprazole-treated patients. A total of 4 patients in the quetiapine group experienced a QTc increase of >40 ms, but no patient had an increase beyond the commonly used cutoff for QTc prolongation of 450 ms. The magnitude of change in QTc was not affected by antipsychotic dose or by patient age, body mass index, or smoking status. Higher baseline potassium levels were associated with greater QTc change in the quetiapine group.

Mean QTd decreased, although nonsignificantly, in both groups by week 12 of treatment. Mean heart rate increased by 11 bpm in the quetiapine group and was unchanged with aripiprazole. Rates of dizziness and tachycardia were higher in the quetiapine group than the aripiprazole group, although the differences were not statistically significant.

***Discussion:*** The QT changes with quetiapine found in the study were small and likely not clinically significant in otherwise healthy patients, however, they may be clinically relevant in patients with significant risk factors for cardiac arrhythmias (e.g., polypharmacy, family history) for whom aripiprazole may be a better option.

Jensen K, Gartner S, Correll C, Ruda D, et al: Change and dispersion of QT interval during treatment with quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: results from the TEA trial. *Psychopharmacology* 2018;235 (March):681–693. From the University of Copenhagen, Denmark; and other institutions. **Funded by the National Research Council for Health and Disease; and other sources. Two of 11 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***Common Drug Trade Names*: aripiprazole—*Abilify*; quetiapine, extended-release—*Seroquel XR***

## 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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## ADHD and Diabetes

In a nationwide longitudinal study, adolescents and young adults with ADHD were more likely than their peers to have onset of type 2 diabetes. Risk was increased regardless of medical comorbidities commonly associated with diabetes—hypertension, dyslipidemia, and obesity—and long-term atypical antipsychotic use.

***Methods:*** Data were collected from Taiwan's national health insurance program. The study cohort comprised all adolescents (aged 10–17 years) and young adults (aged 18–29 years) who received a diagnosis of ADHD in 2002–2009. Each patient was age- and gender-matched with 2 control subjects without ADHD. All patients were required to be free of any type of diabetes at inception of the cohort. Participants in whom type 2 diabetes developed were identified during follow-up lasting through 2011.

***Results:*** The analysis included nearly 36,000 young people with ADHD and 72,000 controls. Study subjects had a mean age of nearly 13 years, and 79% were male. About 60% of those with ADHD were receiving treatment with either methylphenidate or atomoxetine.

Adolescents and young adults with ADHD had an increased incidence of type 2 diabetes compared with controls (0.83 vs 0.21 per 1000 person-years; $p<0.001$; hazard ratio [HR],* 4.01) and a shorter duration from enrollment to diabetes onset (3.17 years vs 4.08 years; $p=0.004$). Patients with ADHD also had an increased prevalence of ADHD-related comorbidities, with HRs ranging from 1.9 to 10.8 for hypertension, obesity, and dyslipidemia. Diabetes risk was greater among patients with these medical comorbidities, but after adjustment for these factors, comedication, and demographics, the risk of type 2 diabetes remained significantly elevated in patients with ADHD (HR, 2.84). Diabetes incidence was not related to use of ADHD medication. Incidence was increased in those who used atypical antipsychotics for ≥1 year (649 patients with ADHD and 55 controls), but not in those who used these medications for shorter periods.

***Discussion:*** Previous research has identified an increased prevalence of obesity and other type 2 diabetes risk factors in young people with ADHD. In the present study, risk of type 2 diabetes was increased overall, and especially in young people who had these risk factors.

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The underlying mechanisms for the association with diabetes may be immunologic dysregulation and proinflammatory cytokine oversecretion.

Chen M-H, Pan T-L, Hsu J-W, Huang K-L, et al: Risk of type 2 diabetes in adolescents and young adults with attention-deficit/hyperactivity disorder: a nationwide longitudinal study. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11607. From Taipei Veterans General Hospital, Taiwan; and other institutions. **Funded by the Taipei Veterans General Hospital. The authors declared no competing interests.**

***Common Drug Trade Names*: atomoxetine—*Strattera*; methylphenidate—*Concerta, Ritalin***

***See Reference Guide.**

## Callous-Unemotional Traits and Family Function

Parents of boys with conduct disorder and a high level of callous-unemotional (HCU) traits had poorer rapport with their children than did parents of boys with conduct disorder and lower levels of these traits (LCU). Families of highly callous and unemotional children also had poorer levels of affective involvement as well as other adverse dynamics. These findings may help clinicians identify targets for family interventions.

***Methods:*** Participant families included a boy, aged 11–16 years, who met screening criteria for a conduct disorder. Boys with autism or Asperger's syndrome, low IQ, or a neurological disorder were excluded. All boys enrolled in the trial completed the Inventory of Callous-Unemotional Traits and those who scored above the median were classified as the HCU (n=35) group. A control group of 31 typically developing (TD) boys was also included in the study. Family function was assessed using the McMaster Family Assessment Device (FAD), which has 7 subscales. Parents were also asked to write a free-form description of their child. These descriptions were then analyzed using qualitative methods to identify major themes.

***Results:*** No differences were observed between conduct disordered youth with HCU and LCU and control families on child age or IQ, child alcohol use, birth order, number of people living in the household, parental psychopathology, child ethnicity, family structure, and parent informant. According to the assessment of family function, families of a child with HCU traits showed poorer levels of affective involvement, general functioning, and role functioning than the other groups. (See table.) However, after adjusting for child ADHD and generalized anxiety disorder, the group effects on general functioning and roles were no longer significant. For some areas of familial function, LCU youths were impaired relative to controls.

**Between-Group Differences in Affective Involvement FAD Scores**

| Study group | Comparison group | Effect size† | Significance |
|---|---|---|---|
| HCU | TD | -1.17 | p<0.01 |
| HCU | LCU | -0.62 | p=0.03 |
| LCU | TD | -0.69 | p=NS |

†Negative effect size* indicates poorer status in the study group

Parents' qualitative descriptions of their child differed depending on the child's level of callous-unemotional traits. Parents of HCU children often described their child as unpredictable and changeable, or loving and bubbly but volatile if stressed. Parents of LCU children described lower levels of changeability, which seemed less problematic. Boys with HCU traits were described as able to turn on the charm to gain something, but those with LCU traits were described as spontaneously kind. Parents typically saw the behavior of boys in the HCU trait group as problematic, while those whose boys had LCU traits normalized the behavior, calling it cheeky or quirky, endearing, or typical of a teenage boy. Although parents of HCU boys cared for their child, there was more sense of a close, affectionate relationship in the families of boys with lower levels.

***Discussion:*** Affective involvement, as operationalized on the FAD, refers to such aspects of function as self-centeredness and using others for personal gain. The study results indicate

children with this characteristic can have a substantial negative impact on collaborative family functioning. General family functioning is probably improved in LCU families by parents' ability to normalize their child's behavior and empathize with the challenges he faces. Role functioning—the extent to which an individual fulfills his functions and responsibilities in the family—was impaired in both clinical groups but especially the families with an HCU child.

Roberts R, McCrory E, Joffe H, DeLima N, et al: Living with conduct problem youth: family functioning and parental perceptions of their child. *European Child & Adolescent Psychiatry* 2018;27 (May):595–604. From University College London; and Cardiff University, U.K. **Funded by the UK Medical Research Council; and an award from the Royal Society. The authors declared no competing interests.**

***See Reference Guide.**

## Pharmacotherapy for School Refusal

Despite the urgent nature and significant consequences of school refusal behavior, there have been very few studies of pharmacological treatments to guide clinical decision-making, according to a literature review. The limited data suggest that pharmacotherapy can be a useful adjunct to psychological therapy in children with comorbid anxiety or depression. Contributing factors unrelated to anxiety and depression, such as bullying, learning disorders, and psychosocial adversity, should also be addressed.

The review included randomized clinical trials and quasi-experimental studies that included ≥10 participants and evaluated pharmacotherapy for school refusal in children and adolescents. The search identified only 6 reports describing 7 studies, most published between the 1970s and 1990s, that included a total of 306 children. In all of the studies, medications were compared with placebo, other drugs, or no pharmacotherapy in children or adolescents who were also receiving psychosocial interventions. All of the studies were underpowered to show a statistically significant benefit of medication, but a few suggested they may have been helpful.

Two studies examined the effect of fluoxetine combined with cognitive behavioral therapy (CBT). In 1 study, fluoxetine was compared with no treatment in 82 children refusing to go to school because of mood disorder. After 12 weeks, fluoxetine was associated with a higher rate of return to school (82% vs 72%), with an effect size* of 0.24 that was not statistically significant. Anxiety, depression, and global illness severity improved equally in both treatment groups. In the second study, 62 patients meeting criteria for anxiety disorders received 12 sessions of CBT in conjunction with fluoxetine, placebo, or no medication. All treatment groups experienced improvement in anxiety and depression. Rates of return to school ranged from 44% to 56% (effect size, 0.34 for improvement in attendance with fluoxetine vs placebo), but the between-group difference was not significant.

Four randomized trials and 1 open-label study examined the effects of tricyclic antidepressants on school refusal. In 1 study, imipramine was superior to placebo in improving school attendance to ≥75% of school hours in children receiving CBT (70% vs 28%; effect size, 1.27; $p<0.001$). However, this study had a relatively small sample size (63 children) and did not correct for multiple statistical comparisons. In 3 additional studies, no positive effects of imipramine on school refusal were found. Clomipramine was also ineffective in a placebo-controlled trial in 46 children receiving tailored individual therapy. Likewise, alprazolam did not produce response in a group of 24 children.

Taken together, these studies indicate that children with school refusal and comorbid depression or anxiety generally had improvement in their school refusal with psychological therapy, with or without pharmacotherapy. Although data on pharmacological treatment are sparse and newer antidepressants (e.g., SSRIs and SNRIs) do not appear to have been evaluated, the authors suggest combined pharmacotherapy and psychosocial treatment may be warranted because of

the serious nature of school refusal along with the fact that children with anxiety disorders make up a large subset of school refusal patients.

Tobon A, Reed M, Taylor J, Bloch M: A systematic review of pharmacologic treatments for school refusal behavior. *Journal of Child and Adolescent Psychopharmacology* 2018; doi 10.1089/cap.2017.0160. From Yale Child Study Center, New Haven, CT; and other institutions. **This review was conducted without external funding. One study author disclosed a potentially relevant financial relationship with a commercial source.**

***Common Drug Trade Names*: clomipramine—*Anafranil*; fluoxetine—*Prozac*; imipramine—*Tofranil***

***See Reference Guide.**

## Nonpharmacological Treatments for ADHD

Despite widespread use, a systematic review of recent studies found little evidence to provide new guidance on use of nonpharmacological interventions for ADHD.

***Methods:*** The review encompassed English-language, controlled or observational studies that were published from 2009 to late 2016 or were included in clinical trial registries. Studies were required to include ≥50 subjects. Participants were children or adolescents, aged ≤17 years, receiving a non-pharmacological treatment for ADHD, either alone or in combination with medication. The treatments included psychosocial, behavioral, or school interventions; cognitive training; biofeedback or neurofeedback; parent behavior training; dietary supplements; elimination diets; vision training; and chiropractic. Comparison treatments could include other nonpharmacological interventions, FDA-approved medications, placebo, usual care, or wait-listing. Study outcomes were changes on standardized symptom scores or progress toward patient-identified goals. Strength of evidence was assessed based on 5 criteria: study limitations, consistency, directness, precision, and reporting bias.

***Results:*** A total of 54 studies were identified. Evidence suggested that in addition to improvements in ADHD symptoms, cognitive behavioral therapy may alleviate depression and anxiety, as well as oppositional-defiant and conduct-disorder symptoms in young people with ADHD. Studies comparing neurofeedback with other nonpharmacological interventions had generally positive results, but no significant differences were found between neurofeedback and methylphenidate (*Ritalin*) or combined treatment. Cognitive training was more effective than a waitlist control, but not more effective than other nonpharmacological treatments. Evidence did not support fatty acids, vitamin D, or zinc supplementation or other dietary/herbal interventions. Findings for child and/or parent training and ginkgo biloba supplementation were mixed. In a single study, an elimination diet had positive results.

***Discussion:*** The authors note several important limitations of the included studies: most had short follow-up periods, there were variations in outcome, and reporting of comparative statistical analyses was inconsistent. While the comparisons were not generally supportive of nonpharmacological treatment, the studies were too small to determine if there is a subgroup of children or adolescents who might benefit from a particular approach.

Goode A, Coeytaux R, Maslow G, Davis N, et al: Nonpharmacologic treatments for attention-deficit/hyperactivity disorder: a systematic review. *Pediatrics* 2018; doi 10.1542/peds.2018-0094. From Duke University, Durham, NC; and other institutions. **Funded by the Agency for Healthcare Research and Quality; and the National Institute of Child Health and Human Development. One of 14 study authors disclosed relevant financial relationships; the remaining authors declared no competing interests.**

## Parent-Only Intervention for Anxiety Disorders

A brief, parent-only group cognitive behavioral training resulted in symptomatic improvement in children with anxiety disorders. Although preliminary, these results support the potential of parent-only anxiety programs without the direct involvement of the child.

***Methods:*** The study enrolled 42 families referred from a university-affiliated outpatient clinic. Children were aged 6–12 years and met DSM-IV-TR criteria for a primary diagnosis of

generalized anxiety disorder, separation anxiety disorder, social phobia, or specific phobia. All children were receiving an SSRI at a stable dose for ≥8 weeks before study entry. Families were randomly assigned to the intervention or to a wait-list control. The active treatment was the parent component of the FRIENDS for Life intervention, which is aimed at empowering parents to recognize and deal with their own anxiety and to use these skills to help their children. The program was offered in 2 groups, each with 10 parents, in 6 weekly sessions.

***Results:*** Of the 20 families randomly assigned to the intervention, 15 participated in enough sessions to be included in the outcome analysis. Children in both groups had a mean age of about 8 years, social anxiety and generalized anxiety disorder were the most common primary diagnoses, and ADHD was the most common comorbidity.

Parents in the intervention group reported significant improvement in family functioning on the Global Relational Assessment of Functioning (p=0.04) and a reduction in their child's emotional symptoms on the Strengths and Difficulties Questionnaire (p=0.007), as well as a significant decrease in their own depression on the Depression-Anxiety-Stress Scale (p=0.006). Clinicians reported that children in the CBT group showed significant improvement in Child Global Assessment Scale scores, compared with controls (p=0.001). Outcomes did not differ between the groups on child self-report measures.

***Discussion:*** The few prior studies of parent-only interventions in childhood anxiety disorder were mostly conducted in preschool children. Results of the present study, including the disagreement between child and parent or clinician ratings of improvement, are consistent with the earlier studies. This may be explained by a lack of sensitivity of measurement tools, reluctance of children to report their anxiety accurately, or a lag in improvement in anxiety management and habituation to fears.

Salari E, Shahrivar Z, Mahmoudi-Gharaei J, Shirazi E, et al: Parent-only group cognitive behavioral intervention for children with anxiety disorders: a control group study. *Journal of the Canadian Academy of Child and Adolescent Psychiatry* 2018;27 (April):130–136. From Azad University of Medical Sciences, Mashad, Iran; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

## Intensive Community Treatment After Discharge

Following hospitalization for a psychiatric emergency, an intensive, community-based treatment to integrate adolescents into outside life was associated with reduced hospital use in the following 6 months. Effects on psychopathology and other study outcomes were mixed.

***Methods:*** The study enrolled 106 individuals, aged 12–17 years, who had received inpatient psychiatric care for ≥72 hours. After stabilization, enrolled patients were randomly assigned to supported discharge service (SDS) or to usual care. SDS was delivered by teams consisting of a child and adolescent psychiatrist, several specialized nursing clinicians, and various administrative and support staff. Clinicians began working with patients within 72 hours after admission and were involved in discharge planning, developing customized care plans, psychological interventions, and assisting the patient with re-integration into school. Special features of the program included a small case load, the team approach, weekly formal and informal team meetings, and work with informal support systems. The duration and intensity of treatment was flexible and based on clinical need. Usual care was delivered by the hospital and by standard community mental health agencies.

The primary study outcomes, assessed at 6 months by blinded raters, were the number of bed-days of inpatient psychiatric treatment; change in the Children's Global Assessment Scale (CGAS), a measure of functioning; and the self-report Strengths and Difficulties Questionnaire (SDQ). In addition to these outcomes, the investigators conducted a cost-benefit analysis using the outcomes of CGAS scores and quality-adjusted life-years (QALYs).

***Results:*** During the 6 months of follow-up, SDS was associated with fewer hospital bed-days than usual care (median, 34 vs 50 days; p=0.04). CGAS and SDQ scores did not differ between the 2 treatment groups at 6 months. However, SDS was associated with a marked difference in the rate of multiple incidents of deliberate self-harm: 24% with SDS and 42% for usual care (odds ratio,* 0.18; p=0.008). Adolescents in the SDS group were also more likely than the usual-care group to have returned to community schools at the end of 6 months (81% vs 51%; odds ratio, 4.14; p=0.001). Results of the economic analysis suggest that SDS is less expensive and more effective than usual care in improving the CGAS score. In terms of QALYs, usual care was not more cost-effective than SDS.

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

Ougrin D, Corrigall R, Poole J, Zundel T, et al: Comparison of effectiveness and cost-effectiveness of an intensive community supported discharge service versus treatment as usual for adolescents with psychiatric emergencies: a randomised controlled trial. *Lancet Psychiatry* 2018;5 (June):477–485. From King's College, London, U.K.; and other institutions. **Funded by the National Institute for Health Research; and other sources. 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.

**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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## Sensory Integration Therapy in ADHD

In a population-based study, young children with ADHD who received sensory integration (SI) therapy were at significantly increased risk of subsequent diagnosis of other psychiatric disorders. According to the study authors, a likely explanation is that receiving SI therapy is a marker for greater risk of later psychopathology.

***Background:*** In Taiwan, where the study was conducted, stimulants are not recommended as the first choice for ADHD therapy in children aged <7 years, and evidence supports a variety of psychosocial approaches. SI therapy is a therapeutic physical activity developed for children with autism, mental retardation, learning disabilities, emotional disturbances, or self-mutilation. The treatment uses controlled sensory inputs to focus children's attention. Parents may seek SI therapy for their children as an alternative, non-stigmatizing, relatively side-effect–free treatment.

***Methods:*** Using a national health claims database, a cohort was identified of children who were aged <8 years and had a new diagnosis of ADHD but no other psychiatric disorder in 2000–2006. A total of 1945 children received SI therapies, which included coordination training, sensory training, activity therapy, balance training, occupational therapy, and sensory-motor training. The comparison group consisted of children from the same cohort who did not receive SI training. Children in the 2 groups were matched by propensity scores* based in part on comorbidity, ADHD medication use, and participation in psychosocial interventions. The primary outcome was the occurrence of subsequent psychiatric disorders during ≤9 years of follow-up.

***Results:*** The majority of children were aged ≥4 years at baseline, >80% were boys, about 40% were receiving ADHD medication, and nearly 30% received psychosocial interventions. The overall incidence of psychiatric disorders was 41% greater in patients who received SI therapy than in those who did not ($p<0.001$). Specifically, rates were significantly higher in the SI group for conduct disorder (hazard ratio [HR],* 2.32; $p<0.001$), emotional disturbances (HR, 1.84; $p<0.001$), and adjustment disorder (HR, 2.27; $p<0.05$). The overall incidence of psychiatric disorders was not affected by gender, age, or baseline comorbidity. Among children who received SI treatment, the overall incidence of other psychiatric disorders during follow-up was

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markedly elevated in children who received only psychosocial interventions (HR, 3.50; p<0.001) and in those receiving ADHD medication only (HR, 1.39; p<0.01), but was only slightly elevated in those who received neither treatment.

***Discussion:*** Evidence supporting SI therapy as a treatment for ADHD is limited, and according to the present results, participation may be detrimental to young children. The study authors acknowledge that it is possible the therapy was used in patients with more severe ADHD-associated behavioral disruptions, which placed them at high risk for other psychiatric disorders and which are not reflected in claims data. However, in the subgroups stratified by presence or absence of these comorbidities, the SI cohort still had higher risk of developing other psychiatric disorders than the comparison cohort. While some parents may prefer SI therapy to the more cumbersome recommended multimodal therapy, they should be advised that without behavioral management and/or pharmacotherapy, SI therapy alone may worsen their child's long-term outcome.

Tzang R-F, Chang Y-C, Kao K-L, Huang Y-H, et al: Increased risk of developing psychiatric disorders in children with attention deficit and hyperactivity disorder (ADHD) receiving sensory integration therapy: a population-based cohort study. *European Child & Adolescent Psychiatry* 2018; doi 10.1007/s00787–018–1171–7. From Mackay Medical College, Taipei, Taiwan; and other institutions. **Funded by the Department of Health, Taiwan; and other sources. One of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

## Extended-Release Amphetamine Suspension

Amphetamine extended-release oral suspension (*Dyanavel XR*) was designed to be ingested easily, to allow individualized dosing, and to provide rapid onset and ≥12 hours of clinical effects. In the manufacturer's laboratory-classroom–based clinical trial, upon which FDA approval was based, the oral suspension produced effects similar to those reported for other long-acting stimulants.

***Methods:*** Study participants were children, aged 6–12 years, with ADHD that required medication. Patients with comorbid Axis I disorders or cognitive impairment were excluded. For the first 5 study weeks, all patients received individually titrated active medication, given once daily in the morning. The final optimized dosage was in the range of 10–20 mg/day. During week 6, patients were randomly assigned to continue their medication for 1 additional week or to switch to placebo. Efficacy was assessed by trained teachers and raters during a day-long observation in a laboratory classroom on the final day of double-blind treatment. Measurement tools were the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale for ADHD symptoms and the Permanent Product Measure of Performance, a timed math test. The study's primary efficacy outcome was change from pre-dose to 4 hours post-dose on the SKAMP Combined score.

***Results:*** Of 108 patients who received treatment, 9 did not complete the study (all for reasons unrelated to medication), and 99 (69% boys; mean age, 9 years) were included in the efficacy analysis. The mean medication dosage was 15.4 mg/day. On the final study day, the SKAMP was administered 8 times in the laboratory-school setting, from 1 to 13 hours post-dose. Active treatment was significantly superior to placebo at each time point. The primary outcome—4-hour SKAMP-Combined scores—significantly favored oral suspension amphetamine over placebo, with a mean treatment difference of 15 points (p<0.0001; effect size,* 1.8). Throughout the day, scores were lower in the amphetamine group for both subscales of the SKAMP: Attention and Deportment. On the math test, children who received active medication attempted and correctly solved significantly more problems (p<0.0001).

During open-label treatment, 5 patients required a dosage reduction because of a moderate adverse event (i.e., insomnia [n=3], dysphoria, or fingernail picking). One-fourth of patients reported decreased appetite, and 1 had a significant 8-lb weight loss.

***Discussion:*** The effect size of oral amphetamine for the SKAMP-Combined score was similar to those of other long-acting stimulants. The safety profile was also similar to comparable drugs.

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

Childress A, Wigal S, Brams M, Turnbow J, et al: Efficacy and safety of amphetamine extended-release oral suspension in children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2018;28 (June):306–313. doi 10.1089/cap.2017.0095. From the Center for Psychiatry and Behavioral Medicine, Inc., Las Vegas, NV; and other sources. **Funded by Tris Pharma, Inc. All 7 study authors disclosed financial relationships with commercial sources including Tris Pharma, Inc.**

***See Reference Guide.**

## DBT for Suicidal Behavior

In a multisite randomized trial, dialectical behavior therapy reduced suicide attempts and self-harm in high-risk adolescents.[1] Differences between DBT and the comparison treatment, manualized individual and group supportive therapy (IGST), were significant during the 6-month treatment period but narrowed between 6 months and 1 year.

***Background:*** A need exists for specific treatments for adolescent self-harm, which increases suicide risk and which may or may not be associated with underlying mental illness. There have been few randomized trials examining the effect of therapies on suicide attempts in self-harming adolescents. The present study replicates an earlier study with a similar design.[2]

***Methods:*** The multicenter trial recruited adolescents, aged 12–18 years, who had ≥1 lifetime suicide attempt, elevated suicidal ideation in the past month, ≥3 lifetime episodes of self-harm (1 in the most recent 12 weeks), and met ≥3 criteria for borderline personality disorder. The 2 randomly assigned, manualized therapies were designed to offer the same treatment exposure: 6 months of weekly individual and group therapy, and parent participation. Adolescents who missed 4 consecutive sessions were considered dropouts but were included in the intent-to-treat analysis. Outcomes—suicide attempts, nonsuicidal self-injury (NSSI), and self-harm—were measured at 3, 6, 9, and 12 months with the Suicide Attempt Self-Injury Interview (SASII) and the Suicidal Ideation Questionnaire Junior (SIQ-JR).

***Results:*** Among the 173 participants enrolled, the mean age was nearly 15 years, 95% were girls, and 53% had a DSM diagnosis of borderline personality disorder. Participants in the DBT group had a higher rate of treatment completion (defined as attending ≥24 sessions) than the IGST group (45% vs 16%; $p<0.001$). On average, the DBT group attended more sessions (20 vs 15; $p<0.001$) and had more weeks in treatment (23 vs 19; $p=0.008$). However, an analysis specifically conducted to determine if between-group differences in outcomes were accounted for by differences in treatment exposure indicated they were not.

During the 6 months of treatment, the percentage of patients free of suicide attempt was significantly higher in the DBT group than in the IGST group (90% vs 78%; odds ratio,* 0.3). Patterns were similar for the odds of being free of NNSI (57% vs 40%; odds ratio, 0.32) and self-harm (54% vs 37%; odds ratio, 0.33). Suicidal ideation, a secondary outcome, also showed a significant advantage for DBT through the end of treatment (effect size,* 0.34; $p=0.03$).

During follow-up, DBT remained superior to IGST for all outcomes with odds ratios of 0.65 for suicide attempt, 0.60 for NSSI, and 0.58 for self-harm, but the between-group differences were no longer statistically significant. The numbers needed to treat* for the DBT group to have an additional adolescent without an outcome compared with the IGST group were 8.5 for suicide attempt, 5.9 for NSSI, and 5.8 for self-harm.

**Editorial.**[3] Taken with the positive results of the earlier study, these results provide sufficient evidence to recommend training and investment in DBT for self-harming girls with emerging borderline personality disorder. However, both studies have limited generalizability because

the overwhelming majority of participants were female and had borderline personality symptoms. It is noteworthy that IGST also produced a large benefit, with fewer sessions; thus whether it might be a cost-effective alternative to DBT should be evaluated.

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

[1]McCauley E, Berk M, Asarnow J, Adrian M, et al: Efficacy of dialectical behavior therapy for adolescents at high risk of suicide: a randomized clinical trial. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.1109. From Seattle Children's Research Institute, WA; and other institutions. **Funded by the NIMH. Ten of 11 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

[2]Mehlum L, et al: Dialectical behavior therapy for adolescents with repeated suicidal and self-harming behavior: a randomized trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 2014;53:1082–1091.

[3]Wilkinson P: Dialectical behavior therapy—a highly effective treatment for some adolescents who self-harm [editorial]. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.1079. From the University of Cambridge and Cambridge and Peterborough NHS Foundation Trust, Cambridge, U.K. **The author disclosed potentially relevant financial relationships.**

***See Reference Guide.**

## Interventions to Improve Self-Regulation

A wide range of interventions to improve self-regulation in children and adolescents are generally beneficial, according to a systematic review and meta-analysis. The improvements in self-regulation appear to translate to improved academic, health, and behavioral outcomes.

***Background:*** Self-regulation includes a range of skills—e.g., controlling emotions, avoiding aggression, and self-directed learning—processes that are often referred to as executive functions. Previous attempts to synthesize the literature on self-regulation interventions have focused on target groups, such as children with ADHD, or specific age groups.

***Methods:*** Randomized and cluster randomized trials of universal interventions to improve self-regulation in persons aged ≤19 years were identified in a literature search. Studies included in the meta-analysis were published in English in a peer-reviewed journal and had no date restrictions. The primary outcome of the meta-analysis was self-regulation skills, which could be evaluated using child-, parent-, or teacher-reported scales or objective task-based measures. Information on health and social outcomes were also reported when available.

***Results:*** A total of 49 studies evaluated 50 interventions in >23,000 participants. The interventions were classified into 5 broad types: curriculum-based, yoga or mindfulness, social/personal skills, exercise-based, and family-based. Curriculum-based interventions, the most common type, were implemented in the classroom, usually by the teacher after receiving special training. Exercise-based interventions were team games, high-intensity interval training, or martial arts. Mindfulness and yoga interventions were administered in school by qualified instructors. Family-based interventions were usually community-based and included such approaches as skill building with parents and after-school programs with siblings. Another group of interventions taught social and personal skills, such as delayed gratification or effortful control, in a group format.

For the meta-analysis, which included 42 interventions with appropriate data, results were positive but highly heterogeneous. An additional meta-analysis was limited to studies that used objective, task-based measures of self-regulation skills. In these studies, the overall effect size* was 0.42. Most intervention types had similar effect sizes (see table), with a somewhat larger effect size for personal-skills training. Interventions were effective in all age

**Effects of universal self-regulation-based interventions**

| Intervention type | Effect size |
|---|---|
| Curriculum-based | 0.34 |
| Yoga or mindfulness | 0.44 |
| Social/personal skills | 0.64 |
| Exercise-based | 0.46 |
| Family-based | NA |

groups and in both community and school settings. In addition, many studies reported beneficial effects on other health and social outcomes, with follow-up ranging from 3 months to 5 years. These effects included improved academic achievement, reduced incidence of conduct disorders, less depression, and less substance use.

***Discussion:*** The present meta-analysis supports the effectiveness of a broad range of interventions, although school curriculum-based programs might be more feasible to provide.

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

Pandey A, Hale D, Das S, Goddings A, et al: Effectiveness of universal self-regulation–based interventions in children and adolescents: a systematic review and meta-analysis. *JAMA Pediatrics* 2018;172 (June):566–575. doi 10.1001/jamapediatrics.2018.0232. From University College London Great Ormond Street Institute of Child Health, London, U.K.; and other institutions. **Funded by the Department of Health Policy Research Programme; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

## Metabolic Effects of Antipsychotic Initiation

Children and adolescents newly started on an atypical antipsychotic for aggression experienced significant increases in total body fat and decreased insulin sensitivity in muscle during the first 12 weeks of treatment. Adverse metabolic changes occurred with all 3 randomly assigned antipsychotics but were greater with olanzapine than aripiprazole or risperidone. These changes occurred with relatively low doses prescribed for an off-label indication.

***Methods:*** Study participants were antipsychotic-naive patients, aged 6–18 years, with clinically significant aggression, whose parents and clinicians had already decided to try antipsychotic treatment. Patients with untreated or undertreated psychiatric conditions were referred back to their treating clinicians for first-line medication trials. Participants were randomly assigned to open-label aripiprazole, olanzapine, or risperidone, reflecting prescribing patterns in 2006–2010 when the study was conducted. Antipsychotic doses were flexibly titrated by the 6th study week. The primary study outcomes, measured by blinded raters at 12 weeks, were total body fat, using dual-energy x-ray absorptiometry (DXA), and insulin sensitivity, using a single-stage hyperinsulinemic-euglycemic clamp procedure with radiolabeled glucose to measure uptake in muscle and hepatic glucose production (glucose rate of disappearance and appearance, respectively). Visceral and subcutaneous abdominal fat were measured with MRI.

***Results:*** The sample included 144 patients (68% male; mean age, 11 years). About 56% had a primary diagnosis of ADHD with irritability and aggression, and half of the sample were receiving stimulants. Mean antipsychotic dosages (risperidone, 1.0 mg/day; olanzapine, 6.3 mg/day; aripiprazole, 6.0 mg/day) were representative of pediatric practice patterns and below the doses typically used to treat psychosis. Patients in all 3 medication groups had similar improvements in irritability, aggression, and overall symptoms by the end of treatment.

After 12 weeks, mean total body fat increased significantly in all medication groups, especially in patients receiving olanzapine. (See table.) The secondary outcome of abdominal fat volume increased in all groups. Mean increases in the visceral fat compartment were comparable for all 3 drugs, but increases in subcutaneous fat were larger with olanzapine ($p<0.001$). Overall combined rates of overweight and obesity increased from the general-population rate of 31% at baseline to 46.5% at 12 weeks.

**Change from baseline to 12 weeks in percentage total body fat by DXA**

| | Mean change± | Effect size* vs olanzapine |
|---|---|---|
| Olanzapine | 4.12% | — |
| Risperidone | 1.81% | 0.74 |
| Aripiprazole | 1.66% | 0.85 |

±p<0.001 compared with baseline for all results

The primary outcome of insulin sensitivity, measured as the insulin-stimulated rate of glucose disappearance, decreased during the 12 weeks in the pooled sample ($p<0.001$; effect size, 0.22). The secondary outcome of insulin sensitivity, measured as the rates of glucose and glycerol appearance, also decreased during the 12 weeks ($p<0.001$; effect sizes, 0.32 and 0.20, respectively. Changes in insulin sensitivity did not differ across treatment groups. Diabetes did not develop in any patient, but 9 showed impaired fasting glucose levels after treatment.

***Discussion:*** This study sample was highly representative of young patients who receive off-label antipsychotic treatment, including the high rate of stimulant use, which apparently offers no metabolic protection. Based on other, long-term studies using less precise measures of adiposity and insulin sensitivity, it seems unlikely that these metabolic changes will reverse with long-term treatment.

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

Nicol G, Yingling M, Flavin K, Schweiger J, et al: Metabolic effects of antipsychotics on adiposity and insulin sensitivity in youths: a randomized clinical trial. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.1088. From Washington University School of Medicine in St. Louis, MO; and Florida Atlantic University, Boca Raton. **Funded by the NIMH; and other sources. Three of 7 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

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

***See Reference Guide.**

## Reference Guide

**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

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

**Odds Ratio:** A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**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.

**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.

**IMPORTANT REMINDER**

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**Important Reminder . . . Delivery of *Child & Adolescent Psychiatry Alerts* is now 100% electronic.**

## Evening Methylphenidate

A new extended-release methylphenidate formulation (*Jornay PM*, formerly HLD200), designed to be administered in the evening in order to control early morning ADHD symptoms, has received FDA approval for use in patients aged ≥6 years. The proprietary delivery system of *Jornay PM* delays initial methylphenidate release for up to 10 hours, followed by a controlled-release throughout the day. Administration timing can be adjusted between 6:30 and 9:30 PM to optimize early-morning and later-day symptom control. In clinical trials, adverse effects of *Jornay PM* were generally those expected with methylphenidate including appetite suppression, weight loss, insomnia, dizziness, and increased blood pressure. Additional adverse reactions specific to *Jornay PM* included headache, psychomotor hyperactivity, and mood swings. Commercial availability of *Jornay PM* is expected in the early half of 2019.

Ironshore Pharmaceuticals announces FDA approval of Jornay PMTM (methylphenidate) extended-release capsules CII for the treatment of ADHD [press release]. George Town, Cayman Islands; Ironshore Pharmaceuticals: August 9, 2018. Available at http://www.ironshorepharma.com/pdf/Ironshore-Announces-FDA-Approval-JORNAY-PM.pdf.

## Bridging Intervention for Adolescent Suicidality After Discharge

Risk for suicidal behavior after hospital discharge is exceptionally high, and there are currently no interventions specifically designed to decrease the risk of suicide attempt during the transition from inpatient to outpatient care. In a preliminary study, a brief inpatient intervention, paired with a post-discharge smartphone app, showed promise in reducing suicide attempts in adolescents hospitalized for suicidality.

***Background:*** The NIMH-funded intervention, As Safe as Possible (ASAP), consists of 4 modules that are completed in the hospital with the aid of a therapist. The intervention includes motivational interviewing, psychoeducation, developing a safety plan, behavioral activation, affect regulation strategies, use of the app, and review of skills with the patient and family. The phone app, BRITE, is meant to be used after discharge. Patients receive daily text messages to rate their level of emotional distress and receive tailored information on distress tolerance and emotional regulation strategies, the personalized safety plan, and clinical contact

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options if needed. The program also includes post-discharge bridging telephone contact with the ASAP therapist, who aids with the transition to a community provider.

***Methods:*** A pilot study of the ASAP intervention was conducted in patients, aged 12–18 years, hospitalized with recent suicidal ideation with a plan or intent or a recent suicide attempt. Patients were randomly assigned to receive ASAP plus treatment as usual or only treatment as usual and were followed for 24 weeks. The primary study outcome was time to suicide attempt.

***Results:*** A total of 66 adolescents participated in the study. They had a mean age of 15 years, 89% were girls, and 77% were white. Most (86%) had a clinical diagnosis of major depression, and 58% had an anxiety disorder. Patients took a mean of 2.7 hours to complete the ASAP inpatient intervention, over a median of 3 sessions. Of the 34 patients who received ASAP, 10 had a session with their families, and 26 had ≥1 bridging telephone call with their therapist.

ASAP was numerically but not statistically superior to treatment as usual at reducing suicide attempts (5 vs 9 attempts, 16% vs 31%) and at prolonging the time to the next attempt (hazard ratio,* 0.49). ASAP had a stronger, but still nonsignificant, effect in patients with a prior suicide attempt (hazard ratio, 0.23). After adjusting for age, the effect was significant (hazard ratio, 0.19; p=0.03). ASAP was not associated with a larger decrease in suicidal ideation than treatment as usual, but patients who received ASAP showed a larger increase in social support.

Most patients in the ASAP group used the smartphone app at least once. They rated their mood a median of 19 times, three-fourths received content about their concerns, and nearly half activated their contacts as part of their safety plan. Frequency of app use was not associated with decreased suicidal ideation or risk of suicide attempt.

Participants gave high ratings for treatment satisfaction whether they received ASAP or only treatment as usual. Adolescents who received ASAP were less likely than controls to participate in outpatient therapy but had otherwise similar levels of service use post-discharge.

***Discussion:*** ASAP was developed to address a critical gap in clinical care between hospital discharge and outpatient care, when risk of a suicide attempt is high. The results of the present study indicate promise, although a larger sample size would be required to show statistical significance.

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

Kennard B, Goldstein T, Foxwell A, McMakin D, et al: As Safe as Possible (ASAP): a brief app-supported inpatient intervention to prevent postdischarge suicidal behavior in hospitalized, suicidal adolescents. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2018.17101151. From the University of Texas Southwestern Medical Center, Dallas; and other institutions. **Funded by the NIMH. Five of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

## Suicide Prevention: Unintended Consequences

According to a literature review, suicide prevention programs can have unintended negative consequences. While these adverse effects are uncommon and do not outweigh the benefits of the programs, they are rarely evaluated, and a more systematic approach to identifying, reporting, and preventing them is needed.

A literature search identified peer-reviewed publications addressing unanticipated consequences of suicide prevention programs, including program evaluations, ecological studies, randomized controlled trials, cohort studies, and case-control studies. Because of the scarcity of articles focusing on youth programs, literature on programs that targeted a broader age range were also included. The review encompassed a total of 22 articles published since 1989, including 17 studies that directly assessed adverse effects.

**Community-based outreach and awareness programs** have been associated with an increase in maladaptive attitudes related to suicide or help-seeking in some young people. A small minority found the information upsetting. These reports are limited to the early years of the review, when representations of suicide were more graphic than they are now. A more recent article showed young people with depression or experiencing suicidality to be less likely to report help-seeking attitudes after being exposed to a media campaign.

**Early identification screening programs** have been assessed in several studies, with mixed results. In 1 study, a minority of students found it distressing to answer questions about suicidal thoughts and self-harm. Several other studies found no evidence of an iatrogenic effect of screening. In another study, students at increased risk for suicide reported less distress after answering screening questions, compared with unexposed high-risk students.

**Skills training programs**, which enhance problem-solving, coping, social, and other skills, have been evaluated in 2 studies that found adverse effects on participants' behavior, possibly due to a contagion effect of clustering high-risk students together.

**Crisis hotline** adverse effects have not been studied in young people. However, studies in adults suggest potential adverse consequences due to the resulting referrals (e.g., high costs, long waits for help, referral for inappropriate services). Although not identified in the studies in the literature review, there is also the potential for adverse consequences when there are insufficient resources to help young people identified as at risk.

Kuiper N, Goldston D, Garraza L, Walrath C, et al: Examining the unanticipated adverse consequences of youth suicide prevention strategies: a literature review with recommendations for prevention programs. *Suicide and Life-Threatening Behavior* 2018; doi 10.1111/sltb.12492. From ICF, Atlanta, GA; Duke University, Durham, NC; and other institutions. **Funded by the Substance Abuse and Mental Health Services Administration. The authors did not include disclosure of potential conflicts of interest.**

## Internet CBT for OCD in Children

In a pilot study, an internet-delivered cognitive behavioral therapy for obsessive-compulsive disorder was feasible and acceptable and had beneficial effects in younger children, while using about one-third the amount of therapist time as face-to-face CBT.

***Background:*** The initial internet CBT program, called BIP OCD was developed by the study authors and evaluated in adolescents. BIP OCD Junior was adapted for use in younger children, mainly by expanding the role of parents. The program uses computer-delivered text, films, illustrations, and exercises focusing on psychoeducation, exposure with response prevention, and relapse prevention. Parents and children, each with a separate login account, work through 12 chapters with tailored content. Throughout the program, a clinical psychologist responds to email queries from family members, usually within 24 hours on weekdays.

***Methods:*** Participants in this study were 11 children (mean age, 9.5 years; 7 girls) who met DSM-5 criteria for OCD and had a baseline Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) score of ≥16. Stable concomitant medication was permitted. The primary study outcome was change from baseline in the CY-BOCS score, with response defined as a ≥35% decrease plus a Clinical Global Impression–Improvement (CGI-I)* score of ≤2, and remission defined as a score of ≤12 plus a CGI-I score ≤2.

***Results:*** All participants completed treatment and a 3-month post-treatment follow-up. The children had a significant mean decrease in the CY-BOCS score from 21 pretreatment to 10 post-treatment ($p<0.001$; effect size,* 1.86). Modest additional decreases were seen at the 3-month follow-up (mean score, 8; effect size, 0.30). Child- and parent-rated OCD symptom severity also improved during treatment. At post-treatment, 8 children (73%) were classified as

responders, including 5 (46%) who met remission criteria. At the 3-month follow-up, 7 children (64%) had achieved remission. Families completed an average of 11 of the 12 chapters. Clinicians had a mean input of 22 minutes per week per participant. Parents and children rated the treatment highly and said they would recommend it to others.

***Discussion:*** Effect sizes in this study were similar to those previously shown in adolescents who participated in BIP OCD and to face-to-face CBT for OCD in children. While the results are positive, the study sample was small, and larger randomized trials are needed.

Aspvall K, Andrén P, Lenhard F, Andersson E, et al: Internet-delivered cognitive behavioural therapy for young children with obsessive-compulsive disorder: development and initial evaluation of the BIP OCD Junior programme. *BJPsych Open* 2018;4:106–112. doi 10.1192/bjo.2018.10. From Karolinska Institutet, Stockholm, Sweden; and other institutions. **Funded by the Swedish Research Council for Health, Working Life and Welfare. This research group developed the iCBT program investigated in the study, but disclosure of additional potential competing interests was not included.**

***See Reference Guide.**

## Cardiovascular Safety of Atypical Antipsychotics

In a large cohort study, initiation of atypical antipsychotic medications was associated with an increased rate of serious cardiovascular events in Medicaid-insured young people. Risk was intensified with increasing antipsychotic doses and with concomitant use of SSRI or SNRI antidepressants.

***Methods:*** The analysis was based on statewide Medicaid claims data from California, Florida, Illinois, and New Jersey. The study cohort consisted of 74,700 patients, aged 5–20 years, who began treatment with an oral atypical antipsychotic between 2005 and 2009. During each month of follow-up, atypical antipsychotic use was categorized as current or former, and rates of cardiovascular events were compared for periods of use and non-use. The primary study outcome was a cardiovascular event (i.e., acute myocardial infarction, stroke, ventricular arrhythmia, aortic or thoracic aneurysm, heart failure, and other cardiovascular events) resulting in inpatient hospitalization or an emergency-department visit.

***Results:*** Most of the study cohort were between the ages of 5 and 14 years (68%) and male (63%); more than half were receiving other psychotropic medications—usually stimulants or antidepressants—before atypical antipsychotics were prescribed. Patients received atypicals for an average of about 10 months and were followed for a mean of 2 years.

A total of 142 cardiovascular events occurred during follow-up. Current atypical antipsychotic use was associated with an increased risk of these events, relative to former use (relative risk [RR],* 1.55). Higher doses conferred greater risk, with an RR of 2.04 in those receiving >3.75 mg/day risperidone (*Risperdal*) equivalents, compared with ≤1.25 mg/day. Duration of exposure was not related to cardiovascular risk. However, during atypical antipsychotic exposure, concomitant SSRI/SNRI use was associated with increased cardiovascular risk (RR, 1.61) compared with non-use. Stimulant use did not affect risk of a cardiovascular event.

***Discussion:*** Second-generation antipsychotic-related risk of serious cardiovascular events has been observed in population-based studies, mostly in adults. Although the incidence of cardiovascular events in this population was low, atypical antipsychotics have been associated with hyperlipidemia, hyperglycemia, type 2 diabetes, prolactin disturbances, and weight gain, all of which are a greater risk for children. Future research should address the comparative risk of different atypical antipsychotics in young patients.

Burcu M, Zito J, Safer D, Magder L, et al: Cardiovascular events following treatment initiation with atypical antipsychotic medications in publicly insured U.S. youth. *Journal of Child and Adolescent Psychopharmacology* 2018; doi 10.1089/cap.2017.0121. From the University of Maryland and Johns Hopkins Medical Institutions, Baltimore, MD. **Funded by the FDA; and the University of Maryland. The authors declared no competing interests.**

***See Reference Guide.**

## Omega-3s for Adolescent Depression

Monotherapy with omega-3 fatty acids was not superior to placebo in a randomized trial in adolescents with depression. This finding is consistent with several large trials in adults but contrasts with the few prior studies in pediatric depression.

***Methods:*** Study participants were unmedicated patients, aged 12–19 years, with a primary diagnosis of major depressive disorder and a current episode duration of ≥6 weeks. Stimulants were the only permitted background psychotropic medication, and psychotherapy could not be initiated or altered during the 10-week study. Active treatment consisted of omega-3 fatty acids with a 2:1 ratio of eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA), titrated to a maximum combined dosage of 3.6 g/day. The primary study outcome was treatment response, defined as a ≥50% improvement from baseline on the Children's Depression Rating Scale-Revised (CDRS-R), correcting for the 17-item base score, or reaching a score of ≤28.

***Results:*** The trial enrolled 48 adolescents (42% boys; mean age, 16 years; mean baseline CDRS-R score, 50). The mean final omega-3 dosage was 3.4 g/day in the study completers: 18 of 21 patients in the omega-3 group and 21 of 27 in the placebo group. The rate of response was 43% in the omega-3 group and 50% in the placebo group, a nonsignificant difference. The 2 groups did not differ in any secondary treatment outcomes, including symptoms that were of special interest: anhedonia, irritability, or suicidality. Fatty acids had no significant adverse effects.

***Discussion:*** It has been proposed that baseline inflammation may moderate clinical response to omega-3 fatty acids in depression. However, in this study, anhedonia, thought to be related to inflammation, did not improve significantly with active treatment. It is possible that omega-3 fatty acid monotherapy may be effective at higher doses, or in less severe depression.

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

Gabbay V, Freed R, Alonso C, Senger S, et al: A double-blind placebo-controlled trial of omega-3 fatty acids as a monotherapy for adolescent depression. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11596. From the Icahn School of Medicine at Mount Sinai, New York, NY; and other institutions. **Funded by the NIH. The authors declared no competing interests.**

***See Reference Guide.**

## Therapeutic Game for Emotional Regulation

In a randomized trial, REThink, an online therapeutic video game, reduced depressive symptoms and emotional problems in healthy children and adolescents.

***Background:*** The REThink game is based on the principles of Rational Emotive Behavioral Therapy (REBT) and Rational Emotive Behavioral Education (REBE). These evidence-based interventions focus on cultivating rational beliefs to replace irrational ones and fostering positive emotions and social behaviors. REThink is a standalone computer game in which the player navigates 7 successive levels with such objectives as identifying cognitive processes, linking them to emotional and behavioral reactions, and learning problem-solving and relaxation skills.

***Methods:*** Study participants were healthy children and adolescents, aged 10–16 years, recruited from a single middle school. They were randomly assigned to play the REThink game, receive standard REBE in a classroom format, or be on a waiting list. The psychological content of REThink and REBE were the same, as was the time spent: 7 modules with 50 minutes per module. Both programs were delivered in school after the end of classes and completed within 1 month. A REBE certified psychologist delivered the didactic program and assisted with the computer game. The primary study outcomes were emotional symptoms, measured with the child version of the Strengths and Difficulties Questionnaire (SDQ), and depressive symptoms, measured with the Early Adolescent Temperament Questionnaire–Revised (EATQ-R).

***Results:*** Of 165 young people who volunteered for the study, 23 dropped out before the initial assessment; the remaining 142 completed the intervention and the pre-, mid-, and post-treatment assessments. The sample consisted of 91 girls and 51 boys; 72% were in grades 5–8, and 28% were in grades 9–10.

Patients in both the REThink and REBE groups demonstrated improvements over time on measures of both emotional symptoms and depression. However, effects were stronger for REThink, and improvements in the REBE group were not statistically significant. Wait-listed patients showed small improvements in depressive symptoms but slightly worsened emotional symptom scores. (See table.) Both the REThink and REBE groups also showed significant improvement in secondary outcomes, including EATQ-R scores for attention and in the control dimension of the Emotion-Regulation Index for Children and Adolescents (ERICA). Only the REThink group showed significant improvement in awareness on the ERICA instrument. There were marginal differences between the groups in SDQ relationship problems and no differences in SDQ prosocial behavior. Participant satisfaction with REThink was higher than REBE mid-treatment, but the 2 were rated as equally satisfactory at the end of treatment.

| Primary study outcomes: Pre- to immediately post-treatment | | | |
|---|---|---|---|
| **Outcome** | **Effect size;* significance vs baseline** | | |
| | REThink | REBE | Waitlist |
| SDQ emotional symptoms | 0.46; p=0.002 | 0.15; p=NS | -0.13; P=NS |
| EATQ-R depressive mood | 0.84; p<0.001 | 0.26; p=NS | 0.12; p=NS |

***Discussion:*** These findings suggest that REThink could have a significant impact on emotional well-being and ability to regulate emotions. The high satisfaction ratings indicate that the REThink game has the potential for wide use. However, the study was conducted in a non-clinical sample, which while it support the use of REThink as a general prevention effort, may not generalize to patients with clinical psychopathology.

***Study Rating*—15 (88%):*** This study met most criteria for a randomized controlled trial; however, the report did not include information on blinding of symptom assessors.

David O, Cardos R, Matu S: Is REThink therapeutic game effective in preventing emotional disorders in children and adolescents? Outcomes of a randomized clinical trial. *European Child and Adolescent Psychiatry* 2018; doi 10.1007/s00787–018–1192–2. From Babes-Bolyai University, Romania. **Funded by the Romanian National Authority for Scientific Research. The authors declared no competing interests.**

***See Reference Guide.**

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**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

**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.

**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.

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

**Study Rating:** A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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## Ketamine for Resistant Depression

In a preliminary study, intravenous ketamine infusion resulted in clinical response in adolescents with resistant depression. Treatment was generally safe and well tolerated.

***Methods:*** Study participants, aged 12–18 years, had depression that had been resistant to ≥2 previous antidepressants and a current score of >40 on the Children's Depression Rating Scale-Revised (CDRS-R). All patients received 6 open-label ketamine infusions over 2 weeks. Dosing for the first 5 patients was based on a formula for ideal body weight (mean dosage, 0.35 mg/kg), but when those patients failed to achieve response, the dosing strategy for the remaining patients was changed to actual body weight and the mean increased to 0.5 mg/kg. The primary outcome measure was the CDRS-R, and patients who met response criteria of a ≥50% decrease in score were invited to participate in 6 weekly follow-up visits and a 6-month final visit. During follow-up, patients received usual care from their own providers. Remission was defined as a CDRS score ≤28, and relapse as a CDRS score ≥50% of the pretreatment baseline.

***Results:*** The 13 patients had a mean age of 17 years; 5 were girls. Of note, the mean body mass index was 30.7. Patients had received an average of 5.7 previous antidepressants, 6 patients had a history of trauma, and 6 had a history of suicide attempts.

In the group as a whole, the mean CDRS-R score decreased from 63.9 to 44.1 following the final infusion (p=0.0004). Of the 8 patients who received actual body-weight dosing, 5 met response criteria and completed 6 weeks of follow-up, 4 of whom also completed the 6-month follow-up. At the post-treatment evaluation, 3 of the 5 achieved remission; 2 of these patients remained in remission at 6 weeks. A third responder reached remission at 6 weeks. The other 2 initial responders experienced relapse at 1 and 2 weeks. At the 6-month evaluation, 2 adolescents remained in remission.

Patients also showed significant improvements at week 6 on secondary outcome measures including the Montgomery-Asberg Depression Rating scale, the Beck Depression Inventory, and the Clinical Global Impression–Severity scale, but not in symptoms of anhedonia. Significant predictors of response were body mass index and the actual ketamine dose. A history of trauma was a trend-level predictor of treatment response.

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Transient blood pressure changes were observed during infusion, but there were no significant changes in heart rate or respiration. Two patients reported feeling dysphoria during infusions, and 3 experienced nausea. One patient who had high levels of suicidal thinking at study entry reported a worsening of suicidal thoughts, although the change was not evident in clinical assessments.

***Discussion:*** Intravenous ketamine has been shown to be effective in resistant depression in adults, in whom dosing based on ideal body weight may be sufficient. The present results suggest actual-body-weight dosing may be more effective in adolescents. Parental concerns about the potential for ketamine to induce substance use disorders were not addressed in the study, nor was the possibility for ketamine to worsen existing substance use disorders in patients with an increased vulnerability. While these preliminary results are positive, they require replication in large, double-blind, controlled trials that address the longer-term effects and safety issues.

Cullen K, Amatya P, Roback M, Albott C, et al: Intravenous ketamine for adolescents with treatment-resistant depression: an open-label study. *Journal of Child and Adolescent Psychopharmacology* 2018;28 (September):437–444. From the University of Minnesota Medical School, Minneapolis; and other institutions. **Funded by the University of Minnesota. The authors declared no competing interests.**

## Asenapine Response in Bipolar Disorder

In patients with bipolar I disorder, the efficacy of asenapine (*Saphris*) was not influenced by the type of current episode or the number of previous episodes, according to a post-hoc clinical-trial analysis.[1] Body weight also did not affect outcome, which suggests there may be no need for weight-based dosing in children and adolescents.

***Background:*** Evidence in adults with bipolar I disorder suggests that treatment outcomes may be related to illness-associated factors such as the number of previous mixed or manic episodes and the characteristics of the current episode (mixed vs pure mania). However, factors that influence treatment response in younger patients have not been well studied. The present post-hoc analysis was undertaken to evaluate predictors of treatment outcome with asenapine in pediatric bipolar disorder.

***Methods:*** The clinical trial compared 3 dosages of asenapine (2.5, 5, and 10 mg b.i.d.) and placebo in patients, aged 10–17 years, with DSM-IV-TR bipolar I disorder.[2] The study's primary efficacy outcome was change from baseline to day 21 in the Young Mania Rating Scale (YMRS); change in the Clinical Global Impression scale for use in bipolar illness (CGI-BP) was the key secondary outcome. Post-hoc analyses were conducted to evaluate the relationship of efficacy to the type of current episode (mixed or manic), the number of previous episodes (<3, 3–5, and >5), and baseline body weight and body mass index, stratified by tertile.

***Results:*** The 403 study patients had a mean age of 14 years and a mean age at onset of 11 years. The majority of patients (56%) were experiencing a mixed episode, and nearly one-third had experienced ≥3 previous manic or mixed episodes. The clinical trial met its primary efficacy endpoint, with statistically significant improvement in the YMRS and the CGI-BP for all 3 asenapine doses, relative to placebo. In the post-hoc analysis, efficacy did not differ as a function of episode type. Patients with either a mixed or manic episode experienced similar decreases in YMRS score (approximate least squares mean changes,* 12–15 points in all groups except those with pure mania receiving 2.5 mg asenapine whose improvement was similar to placebo). The number of previous episodes also did not have a substantial effect on the between-group differences in YMRS change. Least squares mean changes averaged about 6–10 points with placebo, compared with about 10–20 points with asenapine. Asenapine efficacy also did not differ in a consistent manner according to the tertile of body weight. Improvements in

YMRS were generally similar in all groups, except those in the lowest tertile who received the highest asenapine dose, in whom improvements were smaller.

***Discussion:*** The post-hoc analysis of these clinical-trial data indicated that asenapine efficacy did not differ according to gender, age of onset of bipolar disorder, presence or absence of ADHD, or use of stimulants. The results also suggest illness-related factors do not affect efficacy.

[1]Findling R, Earley W, Suppes T, Patel M, et al: Post hoc analyses of asenapine treatment in pediatric patients with bipolar I disorder: efficacy related to mixed or manic episode, stage of illness, and body weight. *Neuropsychiatric Disease and Treatment* 2018;14;1941–1962. From Johns Hopkins University and the Kennedy Krieger Institute, Baltimore, MD; Allergan, Madison, NJ; and other institutions. **Funded by Merck & Co., Inc.; and Allergan. All study authors disclosed potentially relevant financial relationships.**

[2]Findling R, 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;54:1032–1041. See *Child & Adolescent Psychiatry Alerts* 2016;18 (February):8–9.

***See Reference Guide.**

## NMDA Agonist-Enhanced CBT for Panic Disorder

In a placebo-controlled pilot study, D-cycloserine (DCS) did not enhance the effects of intensive cognitive behavioral therapy in adolescents with panic disorder.

***Background:*** This study was an attempt to improve on the efficacy of intensive CBT, which has a long-term response rate of about 72% in adolescents with panic disorder. Augmentation of CBT with DCS has been helpful in adults, but studies in children and adolescents with other anxiety disorders have had inconsistent results.

***Methods:*** The study enrolled 24 adolescents, aged 12–17 years, with a primary diagnosis of DSM-IV panic disorder. Concurrent medication was permitted. All patients underwent intensive CBT, consisting of 6 sessions (2–6 hours each) and 2 days of independent practice, over an 8-day period. Therapy included psychoeducation, cognitive restructuring, interoceptive exposures, in-vivo exposures with the therapist and independently, and relapse prevention. A 30-minute parent component was included at the end of each session. Patients were randomly assigned to receive double-blind 50 mg DCS or placebo, to be taken 1 hour before the start of the 3 exposure-based therapy sessions on days 3–5.

***Results:*** Patients in both groups experienced substantial improvement in all study outcomes, with effect sizes* ranging from 1.64 to 3.58. The addition of DCS did not increase rates of recovery (67% vs 90% for placebo) or response (75% vs 90%). Patients in both groups showed improvement in the number of comorbid diagnoses and in additional measures of panic and anxiety symptoms. DCS did not increase the speed of improvement or increase patient satisfaction with treatment. No adverse effects were reported. At the 3-month follow-up, there continued to be no difference between the DCS and placebo groups on any outcome measure, although 2 patients who received DCS continued to improve after the end of treatment.

***Discussion:*** DCS may enhance not only fear extinction, but also fear-related memories. It is possible that it could be more effective if given only after successful exposures. In addition, the high overall response rate to the intensive CBT may have contributed to the lack of DCS effects.

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

Leyfer O, Carpenter A, Pincus D: *N*-methyl-D-aspartate partial agonist enhanced cognitive-behavioral therapy of panic disorder in adolescents. *Child Psychiatry & Human Development* 2018; doi 10.1007/s10578–018–0837-1. From Boston University and Massachusetts General Hospital, MA. **Funded by the Brain and Behavior Research Foundation. The authors did not include disclosure of potential conflicts of interest.**

***See Reference Guide.**

## tDCS for Anorexia Nervosa

In a pilot study, adding transcranial direct current stimulation to treatment as usual improved weight gain in adolescents with anorexia nervosa.

***Methods:*** Study participants were 23 adolescents (1 boy), aged 10–17 years, with a DSM-5 diagnosis of anorexia nervosa and a body mass index (BMI) of 12–18. The experimental group received tDCS that was excitatory over the left dorsolateral prefrontal cortex (DLPFC; anode) and inhibitory over the right DLPFC (cathode). tDCS was delivered in 20-minute sessions, 3 times/week, for 6 weeks. The comparison group received family psychotherapy, with separate weekly group therapy for adolescents and parents and biweekly family meetings. All participants received an atypical antipsychotic; SSRIs and benzodiazepines were prescribed for some. Both groups received ongoing group and individual psychological support and parent psychoeducation (treatment as usual). Treatment outcomes were assessed using standardized measures of eating disorder pathology as well as anxiety and depression.

***Results:*** Mean BMI increased from 14.7 to 16.6 in adolescents receiving tDCS and from 15.5 to 16.1 in the control group (13% vs 4%; $p<0.01$). These gains in the tDCS group persisted after 1 month of follow-up. Both groups showed significant improvement in the psychopathological rating scales, with no treatment-related difference overall or in any subscale, including drive for thinness, body dissatisfaction, eating disorder risk, low self-esteem, personal alienation, interpersonal insecurity, interpersonal alienation, asceticism, ineffectiveness, interpersonal problems, and global psychological maladjustment. Within the tDCS group, increases in BMI were correlated with improvement in measures of global psychological maladjustment and interpersonal problems, which may suggest tDCS improves cognitive symptoms linked to maladaptive food behavior. tDCS was well tolerated, with few physical complaints and no emergent psychological symptoms. Both treatment groups experienced positive effects on mood and anorexia symptoms, probably due to the nutritional, psychoeducational, and psychopharmacologic interventions common to both.

***Discussion:*** In previous studies, tDCS applied in the opposite direction to the present study was shown to reduce food cravings in overweight individuals and alcohol cravings in patients with alcohol abuse. The authors hypothesize that in these patients, tDCS treatment corrected the right hemisphere hyperactivity believed to underlie the eating disorder, restoring the balance between right- and left-hemisphere activity.

Costanzo F, Menghini D, Maritato A, Castiglioni M, et al: New treatment perspectives in adolescents with anorexia nervosa: the efficacy of non-invasive brain-directed treatment. *Frontiers in Behavioral Neuroscience* 2018; doi 10.3389/fnbeh.2018.00133. From Bambino Gesù Children's Hospital, Rome, Italy. **Source of funding not stated. The authors declared no competing interests.**

## Screening Tools Predict Depression Outcomes

Information on anxiety and substance use collected using screening questionnaires appears to help identify adolescents with depression who are at risk for poor outcomes of collaborative care. Screening tools should not replace a thorough clinical interview, but they can supplement the interviews in identifying young people who may need additional resources to achieve sustained remission.

***Methods:*** Four screening instruments—the CRAFFT substance-use screen, the Mood Disorder Questionnaire–modified for adolescents (MDQ-A), the Patient Health Questionnaire-9 (PHQ-9), and the child-report version of the Spence Children's Anxiety Scale (SCAS-C)—were evaluated as potential predictors of outcomes of a collaborative care program for adolescent depression. The program, called EMERALD, was initiated at a pediatric and adolescent medicine primary

care facility affiliated with the Mayo Clinic. Eligible participants were aged 12–17 years (or 18 if still in high school) and had a new or previous diagnosis of a depressive disorder. Severe comorbid disorders were grounds for exclusion, but adolescents were allowed to participate if they had anxiety disorders, ADHD, substance use disorders not requiring primary treatment, or disruptive behavior disorders. The collaborative care program included depression care management by a registered nurse; supervision by a child and adolescent psychiatrist who recommended medications and psychotherapy; medication management by the primary care physician; and psychotherapy provided by a clinical social worker. Remission was defined as a PHQ-9 score of <5, indicating minimal symptoms. Patients graduated from the program when they achieved this score for 3 consecutive months. Adolescents enrolled in EMERALD for >12 months were assumed to be nonresponders and were offered other forms of care.

***Results:*** The study included a total of 182 patients, of whom 101 achieved remission and 49 graduated from the program. Reasons for failure to graduate were loss to follow-up in 85 patients, treatment failure after 12 months in 25, and the patient's decision in 23.

None of the screening tools were significantly associated with remission. Graduation, however, was associated with lower scores on the CRAFFT and on the SCAS-C. Although both graduates and non-graduates had average CRAFFT scores that were below the clinical threshold, each 1-point increase in this measure was associated with a 62% higher likelihood of failure to graduate (odds ratio,* 1.62; p=0.01). When the SCAS-C was analyzed as a categorical variable, with a score of ≥33 considered positive in boys and ≥39 in girls, scores above the cutoff were associated with a >2-fold higher risk of non-graduation (odds ratio, 2.35; p=0.02).

***Discussion:*** Collaborative care models are being used increasingly to treat complex conditions. The few studies of collaborative care models in child and adolescent depression have had mixed results. Results of the present study suggest that EMERALD, and perhaps other programs, may need to identify adolescents with anxiety and substance use and provide additional interventions from the outset.

Ginsburg A, Stadem P, Takala C, Croarkin P, et al: An examination of screening tools for collaborative care of adolescent depression. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11543. From the Mayo Clinic, Rochester, MN. **Funded by the National Center for Advancing Translational Sciences; and the NIMH. One of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

## ADHD Medications Compared

A comprehensive synthesis of clinical-trial data, based on advanced methodology for network meta-analyses, confirms methylphenidate as the preferred first choice for children and adolescents with ADHD and amphetamines as first-line therapy for adults. There is little evidence of the effects of any medication beyond 12 weeks.

***Methods:*** The analysis was based on a wide-ranging search for studies, with no language restrictions, including dissertations, clinical-trial registries, and data on file at pharmaceutical companies. The studies were double-blind, randomized controlled trials, including parallel-group, crossover, and cluster designs, in children and adolescents (aged 5–17 years) and adults with a primary diagnosis of ADHD. The primary efficacy outcomes of the meta-analysis were change in severity of clinician-rated ADHD symptoms and change in teacher ratings, using standardized rating scales. Tolerability was assessed as the rate of treatment discontinuation. Separate analyses were conducted in children/adolescents and in adults.

***Results:*** The search identified 133 studies, 81 in children and adolescents, 51 in adults, and 1 in patients of all ages, with a total sample size of >14,000 young people and >10,000 adults. Included studies evaluated monotherapy with any of the following medications, compared with

each other or placebo: amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate (including dexmethylphenidate), and modafinil.

All medications were superior to placebo at reducing clinician-rated core ADHD symptoms in children and adolescents, with between-group standardized mean differences* of 0.62–1.02. (See table.) In all age groups, amphetamines were significantly superior to modafinil, atomoxetine, and methylphenidate. In children and adolescents, amphetamines were superior to guanfacine and methylphenidate was superior to atomoxetine. In adults, methylphenidate, atomoxetine and bupropion were superior to modafinil.

| Standardized Mean Differences Between Active Medication and Placebo | |
|---|---|
| Amphetamines | 1.02 |
| Bupropion | 0.96 |
| Methylphenidate | 0.78 |
| Clonidine | 0.71 |
| Guanfacine | 0.67 |
| Modafinil | 0.62 |
| Atomoxetine | 0.56 |

According to teacher ratings of ADHD core symptoms in children (aged ≤11 years), only methylphenidate and modafinil were superior to placebo; no data were available for amphetamines or clonidine.

Guanfacine and amphetamines had higher discontinuation rates than placebo in children and adolescents; all other drugs were at least as well tolerated as placebo. In a post-hoc analysis of individual amphetamines, only lisdexamfetamine was less well tolerated than placebo.

***Discussion:*** Although amphetamines were the most effective agents, they were only marginally more effective than methylphenidate. While amphetamines increased diastolic blood pressure and had higher discontinuation rates, methylphenidate was the only agent found to have better tolerability than placebo. Considering both efficacy and tolerability, methylphenidate emerged as the preferred first-line treatment for ADHD in young patients.

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

Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, et al: Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2018; doi 10.1016/S2215–0366(18)30269–4. From the University of Southampton, U.K.; and other institutions. **Funded by the European Network for Hyperkinetic Disorders; and the U.K. National Institute for Health Research Oxford Health Biomedical Research Centre. Of 19 study authors, 11 disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***Common Drug Trade Names*:** **atomoxetine—*Strattera*; bupropion—*Wellbutrin*; clonidine—*Catapres*; dexmethylphenidate—*Focalin*; guanfacine—*Intuniv, Tenex*; lisdexamfetamine—*Vyvanse*; methylphenidate—*Ritalin*; modafinil—*Provigil***

***See Reference Guide.**

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**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

**Least Squares Mean:** An average estimated from a linear model. In contrast to an arithmetic mean, which is a simple average of the values, least squares means are adjusted for other terms in the model and are less sensitive to missing data.

**Odds Ratio:** A comparison of the probability of an event. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio >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; used for comparison of data obtained using different scales. A value of ≤0.2 is considered a negligible effect, 0.2–0.5 a small effect, 0.5–0.8 a medium effect, and >0.8 a large effect.

**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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## Lisdexamfetamine-Associated Raynaud's Phenomenon

A 16-year-old boy presented with a 3-year history of ADHD that had been temporarily controlled with immediate-release methylphenidate and then an extended-release preparation. Neither agent produced significant adverse effects. When symptom control waned with the extended-release preparation, the patient was switched to 30 mg/day lisdexamfetamine. Symptom control improved, but after 1 week, the patient began to experience symptoms of secondary Raynaud's phenomenon (i.e., pallor and cyanosis of his fingers followed by redness and tingling). Episodes occurred 1–2 times per day, lasted 5–10 minutes each, and were distressing to the patient. He underwent screening for collagen vascular diseases, but no physical cause was uncovered. Because secondary Raynaud's phenomenon has been described with other stimulants, the lisdexamfetamine was stopped and replaced with atomoxetine. The Raynaud's episodes resolved gradually over the subsequent 2 weeks.

According to the Naranjo probability scale,* the association between lisdexamfetamine and Raynaud's phenomenon was probable. This appears to be the first reported case of Raynaud's associated with lisdexamfetamine. Although the reaction is uncommon, clinicians should be aware of the potential as it could adversely affect medication compliance.

Gnanavel S: Lisdexamfetamine and secondary Raynaud's phenomenon [letter]. *Primary Care Companion for CNS Disorders* 2018;20(5):17l02240. From Child and Adolescent Mental Health Services, Northumberland; and Tyne and Wear NHS Foundation Trust, Morpeth, U.K. **The author declared no competing interests.**

***Common Drug Trade Names*: atomoxetine—*Strattera*; lisdexamfetamine—*Vyvanse*; methylphenidate, extended-release—*Concerta*; methylphenidate, immediate-release—*Ritalin***

***See Reference Guide.**

## ADHD History and Neurologic Disorders

In a population-based study, a history of ADHD was associated with a ≥2-fold increased risk of Parkinson's disease and other diseases of the basal ganglia and cerebellum (BG&C). The effect was particularly pronounced in individuals who received stimulants and in those with early-onset BG&C disorders.

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***Methods:*** The analysis was carried out using data from the Utah Population Database, which contains clinical records for 85% of the state's population. The source population for the study was born in 1950–1992 and at least 20 years old during 2011 or the year of last follow-up. The analysis excluded patients with HIV (due to potential for Parkinson-like symptoms) and individuals with a history of amphetamine or methamphetamine abuse, other illicit drug use, or alcohol abuse. Study subjects with ADHD were matched with up to 5 non-ADHD controls, based on gender and birth year. The outcome of interest was a diagnosis, before the end of 2016, of any adult-onset disorder of the BG&C, including Parkinson's disease, secondary parkinsonism, any other disorder of the basal ganglia, and essential tremor.

***Results:*** The ADHD cohort consisted of nearly 32,000 individuals, of whom nearly 5000 (16%) had a history of stimulant treatment (mixed amphetamine salts, 55%; methylphenidate, 39%; both agents, 6%). Median follow-up was 21 years, and during this time, disorders of the BG&C developed in 0.52% of the ADHD cohort and 0.19% of the control group, with median-onset ages of 43 and 45 years, respectively.

After adjusting for tobacco use (which was rare) and psychotic conditions (a proxy for antipsychotic drug exposure), a history of ADHD was associated with increased risk of BG&C disorders (hazard ratio* [HR], 2.4; $p<0.0001$). Risk was further increased in the ADHD cohort by use of stimulants overall (HR, 6.0; $p<0.0001$) and methylphenidate in particular (HR, 8.0; $p<0.0001$). Within the ADHD cohort, risk was increased in patients who received treatment with stimulants versus those who did not (HR, 1.8; $p<0.0001$). Risk was also more pronounced for onset of BG&C disorder before age 50 years (HR, 8.6; $p<0.0001$). The incidence of Parkinson's disease specifically was elevated in the entire ADHD cohort. Those who used medications had a higher likelihood of Parkinson's disease than non-stimulant users, but the difference was not statistically significant.

***Discussion:*** Results of preclinical studies suggest prolonged exposure to amphetamines causes persistent basal ganglia dopaminergic defects. While the present study was not designed to explore biological mechanisms, it is possible that hyperdopaminergic activity, which has been observed in ≥1 model of ADHD, may be a marker for neurons vulnerable to damage. However, according to the authors, the most likely explanation for the association between BG&C disorders and stimulant use is that stimulants are a marker for more severe ADHD.

Curtin K, Fleckenstein A, Keeshin B, Yurgelun-Todd D, et al: Increased risk of diseases of the basal ganglia and cerebellum in patients with a history of attention-deficit/hyperactivity disorder. *Neuropsychopharmacology* 2018; doi 10.1038/s41386–018–0207–5. From the University of Utah School of Medicine, Salt Lake City; and other institutions. **Funded by the National Institute on Drug Abuse; and other sources. The authors declared no competing interests.**

***Common Drug Trade Names*: methylphenidate—*Concerta, Ritalin*; mixed amphetamine salts—*Adderall, Mydayis***

***See Reference Guide.**

## Gender Differences in Risk-Taking Behavior

In a laboratory test of risk-seeking behavior, adolescent boys with conduct disorder showed increased propensity for risk taking compared with typically developing adolescents, but girls with conduct disorder did not. This finding, although preliminary, suggests that different developmental pathways and causal mechanisms may lead to conduct disorder in boys and girls.

***Methods:*** The study enrolled 49 adolescents (23 girls), aged 11–18 years, with conduct disorder, primarily from special education programs, referral units, and services for young offenders. Controls were 51 typically developing adolescents (27 girls). At study entry, all participants completed a diagnostic interview for conduct disorder. Decision making and attitudes toward risk taking were evaluated with the Risky Choice Task, an experimental test of risky decision making and sensitivity to punishing or rewarding outcomes, previously validated in child psychiatric populations.

***Results:*** Adolescents with conduct disorder chose risky options significantly more often than controls (p=0.001). Overall, boys did not make risky choices more often than girls. However, boys with conduct disorder made significantly more risky choices than healthy boys, with a large effect size (partial eta-squared effect size,* 0.278; p<0.001). Girls with conduct disorder did not make more risky choices than control females. The results of the experiment were unchanged after controlling for IQ differences between the groups and for the presence of ADHD symptoms.

***Discussion:*** Previous research on risk taking in adolescents with conduct disorder has been largely limited to boys. In normative populations, males engage in more risk-taking behavior than females. In the present trial, both controls and adolescents with conduct disorder showed a high degree of sensitivity to the expected value and the level of risk of the different trial types.

Sidlauskaite J, González-Madruga K, Smaragdi A, Riccelli R, et al: Sex differences in risk-based decision making in adolescents with conduct disorder. *European Child and Adolescent Psychiatry* 2018;27:1133–1142. doi 10.1007/s00787–017–1024–9. From the University of Southampton, U.K.; and other institutions. **Funded by the European Commission's Seventh Framework Programme for research. Three of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

## Add-On rTMS for Adolescent Depression

In a naturalistic treatment study, add-on repetitive transcranial magnetic stimulation relieved depression and anxiety and had stronger effects in adolescents than in adults.

***Background:*** Studies have demonstrated efficacy of rTMS in adults with major depression, and the treatment is FDA approved for the management of treatment-resistant depression in adults. Evidence for its use in adolescents is limited, and whether efficacy is comparable in adolescents and adults is unknown.

***Methods:*** The study, conducted at the largest psychiatric hospital in China, included inpatients, aged 10–80 years, with a DSM-IV diagnosis of a mood or anxiety disorder. Patients were enrolled in the study if they were experiencing an acute exacerbation of their disorder or if they had a baseline score of ≥14 on the 17-item Hamilton Rating Scale for Depression (HAM-D) or ≥10 on the 14-item Hamilton Rating Scale for Anxiety (HAM-A). Patients were medication free for ≥2 weeks before hospitalization and were started on antidepressant drugs at admission. rTMS was delivered to the left prefrontal cortex at 120% of motor threshold, in 5 sessions per week. Depression and anxiety symptoms, the primary treatment outcomes, were assessed at mid-treatment (after 10 sessions), immediately following the final treatment (after 11–20 sessions), and then 2 and 4 weeks after patients completed rTMS. Response was defined as a ≥50% decrease in HAM-D or HAM-A score, and remission as a final score of ≤7 on either scale.

***Results:*** The study included a total of 117 patients—42 adolescents (aged <18 years), 27 adults (aged 18–59 years), and 48 older patients (aged ≥60 years)—who received ≥10 rTMS treatments and were available for follow-up at 2 weeks. Major depressive disorder was the most common diagnosis (n=92), and <10 patients each had a diagnosis of bipolar disorder, dysthymia, generalized anxiety disorder, an eating disorder, or OCD. A total of 80 patients were taking an SSRI during treatment, and the rest were taking other classes of antidepressant. Participants received a mean of 16 rTMS treatments.

All age groups had significant average improvement in depression and anxiety symptoms at 2 and 4 weeks of follow-up. Among the adolescent patients, mean HAM-D scores decreased from 16.4 at baseline to 6.9 at the 2-week follow-up and to 4.3 at the 4-week follow-up; mean HAM-A scores decreased from 17.6 to 8.2 and 4.4 at 2- and 4-week follow-ups, respectively. Decreases in HAM-D and HAM-A scores were significantly larger in adolescents than in the older age

groups. Adolescents also had significantly higher rates than older patients of HAM-D response (71%) and remission (49%), as well as HAM-A response (65%) and remission (29%) at week 2. Decreases in depression and in anxiety were correlated in older patients, but not in adolescents.

Zhang T, Zhu J, Xu L, Tang X, et al: Add-on rTMS for the acute treatment of depressive symptoms is probably more effective in adolescents than in adults: evidence from real-world clinical practice. *Brain Stimulation* 2018; doi 10.1016/j.brs.2018.09.007. From Shanghai Jiaotong University School of Medicine, China; and other institutions. **Funded by the Ministry of Science and Technology of China; and other sources. The authors declared no competing interests.**

## Guided Internet CBT for Anxiety

Therapist-assisted, internet-delivered cognitive behavioral therapy (ICBT) was an effective treatment for pediatric anxiety disorders in a randomized controlled trial. While ICBT is not recommended as a substitute for face-to-face therapy, it appears to be an acceptable alternative to increase access for those with mild-to-moderate anxiety disorders, as well as those without access to trained therapists.

***Methods:*** The study recruited children, aged 8–12 years, with a principal diagnosis of an anxiety disorder of at least moderate severity. Participants were required to have daily access to the internet and to have a parent or caregiver willing to participate in treatment. Psychotropic use was not an exclusion criteria, but medication was required to have been stable for ≥6 weeks. All participants who met screening criteria were evaluated in person upon enrollment, after 12 weeks of treatment, and at 3 months' follow-up. All treatment was completely web based. The active intervention was based on these authors' BiP Anxiety treatment protocol, in which parents and children work together to complete exposure-based exercises. The active control treatment consisted of internet-delivered child-directed play (ICDP), designed to strengthen the parent-child relationship and teach specific skills. In both interventions, therapist contact consisted mainly of commenting on the parents' worksheets, providing encouragement, answering questions, and reminding those whose participation lagged. The study's primary efficacy outcome was change from baseline on the Anxiety Disorder Interview Schedule for DSM-IV, parent and child versions (ADIS-P/C), administered by blinded raters. A cost-benefit analysis covering a wide range of direct, health care, and societal costs was also conducted. After 12 weeks, participants in the control group were offered ICBT.

***Results:*** Of 131 children who were enrolled and randomized, 10 dropped out of the study and did not provide 12-week data. Participants in both treatment groups showed significant improvements from baseline in ADIS-P/C scores, but the improvement was significantly larger in the ICBT group. Active treatment was also associated with greater improvement in clinician-rated functional impairment and in parent-rated child anxiety symptoms. (See table.) ICBT also produced higher rates of response than ICDP (51% vs 16%; odds ratio,* 5.28; p<0.0001) and a greater proportion of patients who achieved remission, defined as no longer meeting diagnostic criteria for their primary disorder (48% vs 15%; odds ratio, 5.41; p<0.0001). The number needed to treat* was 3 to produce 1 additional remission.

**Outcomes of ICBT vs ICDP at 12 weeks**

| Outcome | Effect Size* | |
|---|---|---|
| | ICBT | ICDP |
| Clinician-assessed severity rating | 1.22 | 0.72 |
| Clinician-assessed global functioning | 0.80 | 0.42 |
| Child-rated anxiety symptoms | 0.58 | 0.38 |
| Parent-rated anxiety symptoms | 1.12 | 0.44 |

Children who initially received ICBT continued to improve, with 40 of 57 (70%) meeting

remission criteria at 3 months. Of the 46 children with available data who crossed over from control treatment to ICBT, 24 (52%) achieved remission after ICBT and 28 (60%) had remission at 3 months.

A large majority of parents in the ICBT group (88%) reported that they were satisfied with the treatment, compared with 42% in the ICDP group. Average therapist time was 25 minutes per week with ICBT and 9 minutes per week with ICDP. Mean total societal costs per patient were lower with ICBT than ICDP, with savings in all categories of cost except for therapist time.

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

Jolstedt M, Wahlund T, Lenhard F, Ljotsson B, et al: Efficacy and cost-effectiveness of therapist-guided internet cognitive behavioural therapy for paediatric anxiety disorders: a single-centre, single-blind, randomised controlled trial. *Lancet Child and Adolescent Health* 2018; doi 10.1016/S2352-4642(18)30275-X. From the Karolinska Institutet, Stockholm, Sweden; and other institutions. **Funded by the Swedish Research Council for Health, Working Life and Welfare; and Stockholm County Council. Six of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

## Ecopipam for Tourette Syndrome

The investigational dopamine $D_1$ receptor antagonist ecopipam reduced symptoms of Tourette syndrome in a crossover study in children and adolescents.[1] Ecopipam treatment did not cause weight gain or movement disorders, which are adverse effects of the $D_2$ receptor antagonists commonly used to treat this disorder.

***Methods:*** Study participants were aged 7–17 years, weighed ≥44 lbs, and met DSM-5 criteria for Tourette syndrome. Participants were required to have both motor and vocal tics and to meet minimum severity criteria. Patients with OCD or ADHD could enroll, but all medications had to be stable and use of dopaminergic drugs, including stimulants, was not permitted. Patients received double-blind ecopipam or placebo for 30 days, followed by a 3-day taper and a 10-day washout, and then crossover to the alternate treatment. Ecopipam dosage was weight-based with targets of 50 mg/day in children <77 lbs and 100 mg/day in those weighing more. The primary efficacy outcome was change from baseline in the Yale Global Tic Severity Scale (YGTSS) total tic score.

***Results:*** A total of 40 patients (mean age, 13 years; 80% male) participated in the study. All received their target dose of ecopipam, and 38 completed the trial. Mean YGTSS scores were 33 prior to ecopipam treatment and 34 prior to placebo. After 30 days of treatment, ecopipam was associated with larger reductions in score than placebo (5.6 points vs 3.4 points; p=0.03). The between-group difference reached statistical significance at day 16 and continued through day 30. Ecopipam was superior to placebo for both the motor and phonic YGTSS subscales and the YGTSS Impairment score at day 16, although only the difference in motor tics remained statistically significant at day 30. According to Clinical Global Impression (CGI)–Severity ratings, the proportion of patients severely affected decreased from 98% at baseline to 55% after ecopipam treatment and remained at 80% after placebo treatment. CGI–Improvement ratings indicated much improvement or better in 48% after ecopipam and in 25% after placebo. Ecopipam did not affect symptoms of OCD or ADHD and was not associated with clinically meaningful lab or electrocardiogram abnormalities or weight gain. One patient withdrew from ecopipam treatment because of worsening tics.

***Discussion:*** Tics share characteristics of both intentional and automatic actions. The $D_1$ receptor has an excitatory function in the circuits that underlie these types of movement, and the $D_2$ receptor has an inhibitory function. Theoretically, blocking either pathway should reduce hyperkinetic movements. $D_2$ blockers are commonly used to treat Tourette syndrome,

but their use is limited by weight gain, cognitive dulling, dysphoria, and acute dystonic reactions. Ecopipam, the first selective $D_1$ receptor blocker to be evaluated in Tourette, previously showed promise in an open-label study in adults.[2]

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

[1]Gilbert D, Murphy T, Jankovic J, Budman C, et al: Ecopipam, a D1 receptor antagonist, for treatment of Tourette syndrome in children: a randomized, placebo-controlled crossover study. *Movement Disorders* 2018; doi 10.1002/mds.27457. From Cincinnati Children's Hospital Medical Center, OH; and other institutions. **Funded by Psyadon Pharmaceuticals, Inc. Nine of 11 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Gilbert D, et al: A D1 receptor antagonist, ecopipam, for treatment of tics in Tourette syndrome. *Clinical Neuropharmacology* 2014;37 (January/February):26–30.

***See Reference Guide.**

## Reference Guide

**Effect Size (Cohen's D):** 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.

**Effect Size (Partial Eta-Squared):** The effect size represents the amount of change in outcome that can be attributed to treatment. When using the partial eta squared statistic, 0.01 indicates a small effect, 0.06 a medium effect, and 0.14 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

**Naranjo Probability Scale:** A 10-point scale used to determine the likelihood that an adverse reaction is caused by an implicated medication. Based on scores, associations are considered doubtful, possible, probable, or highly probable.

**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 the treatment.

**Odds Ratio:** A comparison of the probability of an event. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio >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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## Long-Term Safety of Guanfacine

Extended-release guanfacine (*Intuniv*), a nonstimulant treatment for ADHD, was well tolerated in a 2-year, manufacturer-sponsored safety trial at dosages up to 7 mg/day, a higher dosage and longer exposure than previously reported. The study, conducted in Europe, specifically examined adverse effects that are identified as important by the European Medicines Agency's risk management program: sedative events, low blood pressure, and weight gain.

***Methods:*** The study was an open-label, single-arm extension trial, conducted in patients previously enrolled in 1 of 2 randomized controlled trials of the drug. Participants were children (aged 6–12 years) and adolescents (aged 13–17 years) with ADHD of at least moderate severity. After a taper of medications from the previous trial, all patients received guanfacine, starting at 1 mg/day and increased by 1 mg/week to a maximum of 4 mg/day in children and to 4–7 mg/day in adolescents. Treatment consisted of up to 7 weeks of dose optimization, 95 weeks of dose maintenance, and 2 weeks of dose tapering. The primary study objective was to observe the safety and tolerability of the drug, but efficacy was also assessed as a secondary outcome.

***Results:*** A total of 214 patients (61% children) were included in the safety analysis. Of these, 7 did not complete treatment because of an adverse event, 19 because of lack of efficacy, and 55 for other reasons, leaving 133 (62%) to complete the study. The median daily guanfacine dose was 4 mg/day, and patients were exposed for a mean of 565 days.

An adverse event related to guanfacine occurred in 62% of patients, and 27% required a dose reduction. A total of 125 sedative adverse events—somnolence, sedation, or hypersomnia—were reported in 81 patients (38%). These events led to discontinuation in 2. Sedative events generally occurred during treatment week 3 or 4 and had a mean duration of 11 days.

Patients experienced initial decreases in heart rate and blood pressure, which gradually returned to pretreatment levels. No patient experienced clinically important QTc interval prolongation. Mean standardized scores for height, weight, and body mass index (BMI) remained stable throughout the study. Most patients remained in their initial BMI percentile

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category. Of 157 patients considered to be at a healthy weight at study entry, 137 (87%) remained in the healthy weight category. Of 45 initially overweight patients, 12 (27%) achieved a healthy weight and 10 (22%) met criteria for obesity.

Guanfacine was associated with a statistically significant improvement in ADHD symptoms, measured with the ADHD Rating Scale-IV and Clinical Global Impression–Severity scale. Most of the improvement was evident in weeks 1–4. The proportion of patients rated as normal or borderline mentally ill increased from 1% at baseline to 46% at final assessment.

***Discussion:*** The results of this study confirm the long-term safety of guanfacine in young patients with ADHD. Efficacy was similar to that previously reported in shorter-term trials, and no new safety signals were detected.

Huss M, Dirks B, Gu J, Robertson B, et al: Long-term safety and efficacy of guanfacine extended release in children and adolescents with ADHD. *European Child & Adolescent Psychiatry* 2018;27 (October):1283–1294. doi 10.1007/s00787-018-1113-4. From Johannes Gutenberg University Mainz, Germany; and other institutions. **Funded by Shire Development LLC. All 6 study authors disclosed relevant financial relationships with commercial sources, including Shire.**

## Online Emotion Regulation Therapy for NSSI

In a pilot study, emotion regulation individual therapy for adolescents (ERITA), delivered online by computer and mobile app, was a feasible and promising treatment for nonsuicidal self-injury.

***Background:*** ERITA, which was developed by these researchers, is adapted from a manualized treatment for NSSI in adults. It was previously pilot-tested as a face-to-face intervention in adolescents with large positive effects on NSSI frequency, emotion dysregulation, self-destructive behaviors, and global functioning. Given the efficacy of in-person ERITA and the potential advantages of online therapist-guided interventions, the program was adapted to facilitate online delivery.

***Methods:*** Participants were 25 self- or clinically-referred adolescents (aged 13–17 years; 19 girls), who met diagnostic criteria for NSSI, had a self-injury episode in the past month, and had a parent willing to participate in treatment. The adolescents were given 12 weeks to complete 11 modules, delivered fully online and consisting of educational texts, animated films, illustrations, case examples, and interactive exercises. The program covers content areas including impulse control, emotional awareness, emotional willingness and approach, and emotion regulation strategies. Each participant was also given a mobile app to report on emotions and behaviors, receive reminders and additional instruction, and have access to their individual crisis plan. Parents concurrently participated in a 6-module online program. The study's primary efficacy outcome was change from baseline to posttreatment in the frequency of NSSI.

***Results:*** Patients completed a mean of 9.7 modules, and parents a mean of 5.2. Therapists spent an average of 5.2 hours monitoring and providing feedback for each family. Patients rated their alliance with the therapist as very high, and their satisfaction with the treatment as acceptable, a rating similar to the face-to-face ERITA trial.

Overall, NSSI episodes were reduced by 55% from pre- to posttreatment ($p<0.001$; effect size,* 0.88), and a further 52% reduction from posttreatment to the 3- and 6-month follow-up. The average number of NSSI episodes was 10 per month pretreatment, 4.5 posttreatment, 2.2 at 3 months, and 3.1 at 6 months. The proportion of patients abstinent from NSSI in the past month increased from 0 to 28% posttreatment, 48% at 3 months, and 40% at 6 months ($p=0.007$). Patients also experienced improvement in emotion regulation (effect size, 0.75), global functioning (effect size, 1.01), and a small but significant improvement in psychological flexibility (effect size, 0.27). Parents' distress about their child's NSSI did not improve during treatment, but their punitive reactions decreased and support and encouragement improved.

***Discussion:*** Few treatments have been developed specifically for adolescent NSSI, and access to empirically-supported options for this behavior is limited. The present results support the feasibility, acceptability, and efficacy of online ERITA, as well as the mediating role of emotion regulation in NSSI improvements. Further study of online ERITA in a larger-scale randomized controlled trial with a more diverse population appears to be warranted.

Bjureberg J, Sahlin H, Hedman-Lagerlöf E, Gratz K, et al: Extending research on Emotion Regulation Individual Therapy for Adolescents (ERITA) with nonsuicidal self-injury disorder: open pilot trial and mediation analysis of a novel online version. *BMC Psychiatry* 2018; doi 10.1186/s12888-018-1885-6. From the Karolinska Institutet; and Stockholm Health Care Services, Sweden. **Funded by the National Self Injury Project in Sweden; and other sources. Two of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

## Parent-Child Therapy for Early Childhood Depression

In a single-blind randomized trial, a parent-child psychotherapy for early childhood depression was effective in children as young as age 3 years.

***Methods:*** Parent-Child Interaction Therapy (PCIT) is a validated, widely used treatment for early childhood behavioral problems. Participants in the present study were offered a modified version of this therapy that added a novel emotion development module (PCIT-ED). Children in the control group were placed on a waiting list and eventually offered the therapy. Active treatment consisted of the standard 12 sessions of PCIT, followed by an additional 8-session emotional development module, using the same techniques as PCIT (teaching of parents, followed by coaching the parent via a bug-in-the-ear device) to enhance the child's emotional competence and emotion regulation. Participants were children, aged 3–6 years, recruited from preschools, day care centers, and clinical sources, who met criteria for early-onset depression on the Preschool Age Psychiatric Assessment. The primary study outcome was a DSM-5 diagnosis of major depression at the end of treatment.

***Results:*** A total of 229 parent-child dyads participated in the trial. Outcomes were assessed a mean of 24 weeks after baseline in the PCIT-ED group and 20 weeks in the control group. At this point, 22% of the PCIT-ED group and 75% of controls still met diagnostic criteria for depression (odds ratio,* 12.15; $p<0.001$). Remission—defined as no longer meeting the diagnostic criteria, plus a ≥50% decrease in depression scores on the Preschool Feelings Checklist—occurred in 73% of the PCIT-ED group and 23% of controls (odds ratio, 0.10; $p<0.001$). Additional positive results of PCIT-ED included reduced functional impairment, overall clinical improvement, and reduced anxiety disorder and oppositional defiant disorder comorbidities. Children who received active treatment also showed improvements in parent-rated emotional functioning, with less emotional lability and more emotion regulation. Parents had decreased personal symptoms of depression and parenting stress and employed more parenting techniques that focused on emotion reflection and processing. The treatment was rated by parents as highly acceptable.

***Discussion:*** PCIT-ED appears to be the first empirically supported psychotherapy specific to early childhood depression. Important advantages are that it is low risk, can be delivered by master's level therapists, and is relatively brief and manualized.

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

Luby J, Barch D, Whalen D, Tillman R, et al: A randomized controlled trial of parent-child psychotherapy targeting emotion development for early childhood depression. *American Journal of Psychiatry* 2018;175 (November):1102–1110. doi 10.1176/appi.ajp.2018.18030321. From Washington University in St. Louis, MO. **Funded by the NIMH. Two of 5 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

## Psychotherapy for Acute Anxiety Disorders

Group cognitive behavioral therapy (CBT) may be the best initial choice of therapy for anxiety disorders in children and adolescents, according to a network meta-analysis.*

***Methods:*** A comprehensive literature search identified randomized controlled studies of structured psychotherapies, in any language, either published or made available in clinical trial databases through November 2017. Psychotherapies were considered structured if they either were manualized for therapists or had a manual for self-administering participants (e.g., Internet or bibliotherapy). Participants had DSM-5 anxiety disorders and were aged ≤18 years upon enrollment. The investigators compared different modalities (face to face or Internet), conditions (child, parental involvement, or parent-only), and formats (group, individual, or mixed). Different control conditions were compared separately and included: no treatment, treatment as usual, waiting list, and psychological placebo (i.e., considered inactive by researchers but presented to participants as an active therapy). The primary efficacy outcome was change from baseline to the end of treatment and the end of follow-up in anxiety symptoms, measured on any valid continuous scale. Acceptability was measured as the proportion of patients discontinuing treatment.

***Results:*** The investigators identified 101 clinical trials involving 6625 patients and examining 2 types of therapy in 11 formats: behavioral therapy (group, combined individual and group, and individual with parent involvement) and CBT (group, group with parental involvement, individual, individual with parental involvement, combined individual and group, Internet-assisted, parent-only, or bibliotherapy). The difference between CBT and behavioral therapy was the inclusion of cognitive restructuring in the latter. Three-fourths of the studies included patients with mixed anxiety disorders. A total of 20 trials included only children, 49 only adolescents, and 32 included both age groups. The median patient age was 11 years, mean number of sessions was 12, and median treatment duration was 12 weeks.

In the network meta-analysis, all psychotherapies were more effective post-treatment than waitlist control (see table for efficacy ranking), but only group CBT was more effective than all control conditions and other psychotherapies. Compared with other therapies involving human contact, group CBT was associated with a number needed to treat (NNT)* of about 5. The NNT for comparison with interventions without human contact (i.e., Internet and bibliotherapy) was about 3.

At the end of follow-up, all therapies, including psychological placebo, were more effective than the waitlist control or no treatment. The most effective modalities were parent-only CBT (67.9%), individual behavior therapy with parent involvement (66.1%), and internet-assisted CBT (65.6%). Bibliotherapy CBT was the least well tolerated psychotherapy indicated by the highest rate of discontinuation.

**Post-Treatment Efficacy Ranking of Psychological Therapies for Anxiety**

| Treatment Group | Likelihood of Efficacy (SUCRA*) |
|---|---|
| Group CBT | 93.4% |
| Group behavioral therapy | 86.1% |
| Individual behavioral therapy with parent | 69.9% |
| Individual CBT | 69.5% |
| Group CBT with parent | 69.3% |
| Individual CBT with parent | 54.8% |
| Individual plus group behavioral therapy | 45.7% |
| Parent-only CBT | 42.2% |
| Bibliotherapy CBT | 42.0% |
| Individual plus group CBT | 40.8% |
| Psychological placebo | 37.9% |
| Treatment as usual | 33.5% |
| Internet CBT | 33.4% |
| No treatment | 29.3% |
| Waitlist | 2.4% |

***Discussion:*** Interpretation of these findings is limited by the small number of trials for each treatment or control condition, poor methodology and risk of bias of many studies, and the potential for publication bias. However, the results do provide some support for the suggestion that group therapies might be the best initial therapy for anxiety disorders in children and adolescents and that therapies requiring a certain level of cognitive maturity may be less effective in children than adolescents.

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

Zhou X, Zhang Y, Furukawa T, Cuijpers P, et al: Different types and acceptability of psychotherapies for acute anxiety disorders in children and adolescents: a network meta-analysis. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.3070. From the First Affiliated Hospital of Chongqing Medical University, China; and other institutions. **Funded by the NIHR Oxford Cognitive Health Clinical Research Facility; and other sources. Seven of 17 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

## Conduct Problem Trajectories

Research has identified 3 trajectories of conduct problems: early onset persistent (EOP), with onset in childhood; adolescent-onset (AO); and childhood-limited (CL), which appears to remit in adolescence or adulthood. According to a meta-analysis, all 3 subtypes are associated with poorer psychosocial outcomes in early adulthood, compared with individuals without conduct problems. The 3 groups form a "hierarchy of risk," with the worst outcomes in the EOP group.

***Methods:*** A systematic literature review identified longitudinal studies that: compared subtypes of conduct disorder or conduct problems based on age of onset; used growth models to compare outcomes; and assessed outcomes beyond the age of 16 years. A total of 8 different adverse outcomes were evaluated: mental health (depression), cannabis use, alcohol use, self-reported aggression, criminal/antisocial behavior, poor general health, poor education, and poor employment outcome.

***Results:*** The search identified 13 studies with nearly 10,700 subjects. Most studies compared outcomes in all 3 trajectory groups with a reference category of persons with a low level of conduct problems. Study subjects were enrolled at a mean age of 5.5 years (range, 4–9 years) and followed until a mean age of 22 years (range, 17–32 years).

For nearly all outcomes, the EOP group had the highest risk of a poor result, with odds ratios* ranging from 1.85 to 5.40, compared with control subjects with "low" conduct problems. (See table.) The AO group had the highest odds ratio for cannabis use (3.78) and a similar odds ratio to the EOP group for poor general health outcomes. Among subjects with conduct problems, the EOP group was not at statistically significantly higher risk than the AO

**Odds Ratios of Negative Outcomes in Conduct Problem Subgroups vs Controls**

| | # Studies | EOP | AO | CL |
|---|---|---|---|---|
| Depression | 7 | 2.24 | 1.58 | 1.29 |
| Cannabis use | 7 | 3.34 | 3.78 | 1.14 |
| Alcohol use | 5 | 1.85 | 1.72 | 1.14 |
| Self-reported aggression | 7 | 5.4 | 3.55 | 1.75 |
| Criminal/antisocial behavior | 6 | 3.18 | 2.29 | 1.28 |
| Poor general health | 4 | 2.35 | 2.38 | 1.36 |
| Poor education | 6 | 4.14 | 2.35 | 1.83 |
| Poor occupational outcome | 5 | 2.0 | 1.22 | 1.14 |

group for any of the outcomes studied. However, the EOP group did have significantly worse outcomes than the CL group for mental health, cannabis use, self-reported aggression, criminal behavior, and poor employment outcome. The AO group differed statistically from the CL group only for cannabis use.

***Discussion:*** Early-onset persistent conduct problems are thought to be associated with familial predisposition, neuropsychological deficits, and temperamental hyperactivity, while AO problems are believed to develop through association with delinquent peers or status-seeking. The observed persistence of problems in the AO group conflicts with reports that problem behavior in adolescence is transient and relatively normative. The more recently described CL type is believed to be associated with near-zero levels of problem behavior by adolescence or adulthood; however, the present observations suggest that some problems with educational outcomes and aggression do persist into early adulthood.

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

Bevilacqua L, Hale D, Barker E, Viner R: Conduct problems trajectories and psychosocial outcomes: a systematic review and meta-analysis. *European Child & Adolescent Psychiatry* 2018;27 (October):1239–1260. From University College London, U.K.; and other institutions. **Funded by the Department of Health Policy Research Programme; and other sources. The authors declared no competing interests.**

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**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

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

**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 the treatment.

**Odds Ratio:** A comparison of the probability of an event. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio >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.

**Surface under the cumulative ranking curve (SUCRA):** A numeric presentation of the overall ranking of treatment efficacy. SUCRA values range from 0 to 100%, with higher values indicating better efficacy.

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## ADHD and Age at School Enrollment

According to an analysis of data from a large national insurance database, rates of ADHD diagnosis and treatment are higher among children with a birthday in the month before the age cutoff for kindergarten than in their older peers. This finding implies that behavioral symptoms may be attributed to ADHD in the younger children, rather than being recognized as associated with their younger age.

***Methods:*** The investigators analyzed data from a large claims database that covers all 50 U.S. states and includes commercial payers but not Medicaid claims. The nearly 408,000 children in the study cohort were born between 2007 and 2009 and had completed ≥1 year of elementary school by 2015, the end of the study. In the 18 states that enrolled children with a birthday cutoff of September 1, rates of ADHD diagnosis and treatment were compared between children born in August (n=36,319), the youngest in their class, and children born in September (n=35,353), the oldest. The analysis was repeated in other consecutive birth-month cohorts of school-aged children and in children aged <4 years (before school entry) with August and September birthdays.

***Results:*** Among the school-aged children in states with a September 1 kindergarten entry cutoff, ADHD was diagnosed at a 34% higher rate in children born in August than in those born in September (85 vs 64 per 10,000 children, respectively). In states with the cutoff, the gap in ADHD diagnosis between the 2 ends of the cohort was larger in boys and smaller, lacking statistical significance, in girls. Children born in August also had a 32% higher rate of treatment with a stimulant (53 vs 40 per 10,000 children). Among those receiving medication, August-born children received an average of 120 more days of medication than those born in September.

When the analysis was repeated in states that did not have a September 1 cutoff, the differences between August- and September-born children were smaller and not statistically significant. There were also no significant differences in diagnosis or treatment rates between any other consecutive pairs of months or in August versus September birth groups before school-entry age.

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***Discussion:*** These observations emphasize the importance of the context of other children's behavior in influencing teachers' identification of ADHD. Considering the age of a child relative to their peers may help clinicians assess whether behaviors reported by teachers and parents are indicative of ADHD.

Layton T, Barnett M, Hicks T, Jena A, et al: Attention deficit-hyperactivity disorder and month of school enrollment. *NEJM* 2018;379 (November 29):2122–2130. doi 10.1056/NEJMoa1806828. From Harvard Medical School, Boston, MA; and other institutions. **Funded by the NIH. Two of 4 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

## TBI and Neurodevelopmental Disorders

Traumatic brain injury in early childhood was associated with subsequent development of ADHD, autism spectrum disorder, and developmental delay in a large cohort study.

***Background:*** Previous studies of TBI and ADHD have focused on school-aged children and adolescents. Because a diagnosis of ADHD is usually made in children aged 3–6 years, the likely sequence of events was previously unresolved. Theoretically, ADHD increases the risk of accidents and accompanying injury. No large-scale epidemiologic study of the incidence of autism following TBI was previously available. Although studies of the causes of autism have focused on genetics, environmental factors such as TBI should not be ignored.

***Methods:*** The analysis was based on Taiwan's National Health Insurance Research Database. The TBI cohort consisted of all children aged <3 years who had a TBI diagnosed clinically or by brain imaging in 1998–2008 and who had no previous diagnosis of ADHD, autism, or developmental delay. Members of the cohort were age- and gender-matched with 4 controls who had not experienced a TBI and had no neurodevelopmental disorder. Children were followed through 2011.

***Results:*** About 7800 children were included in the TBI cohort. The injuries occurred at an average age of 1.5 years and were mild in 94% of cases. TBI was associated with significantly increased incidence of each type of neurodevelopmental disorder. The incidence of ADHD during follow-up was 6.2% in the TBI cohort and 4.0% in controls ($p<0.001$). Similar trends were observed for autism spectrum disorders (incidence, 0.8% vs 0.4%; $p<0.001$) and developmental delay (incidence, 2.9% vs 1.1%; $p<0.001$). Neurodevelopmental disorders were identified at a significantly earlier age in the TBI cohort than in the control group, on average about 1–1.5 years. After adjustment for potential confounding factors—demographic data and comorbid perinatal conditions such as infections, birth trauma, and birth asphyxia—risk for each of the diagnoses was significantly elevated in children who had experienced a TBI, compared with controls, with hazard ratios* of 1.59 for ADHD, 2.06 for autism spectrum disorders, and 2.61 for developmental delay.

Children injured before age 1 year had a higher incidence of each of the 3 disorders than children injured when they were older. Repeated TBI increased risk of ADHD and developmental delay to a larger extent than a single TBI. A longitudinal analysis showed that children whose TBI occurred before the age of 3 years continued to have higher cumulative incidence of the 3 disorders throughout the subsequent ≥10 years.

***Discussion:*** The mechanism underlying the association between TBI and neurodevelopmental disorders is unclear. However, MRI studies have shown alterations in cortical thickness and activation following brain injury. In addition, brain injury may impair theory of mind, which develops at an early age and has been suggested to play a role in neurodevelopmental disorders.

Chang H-K, Hsu J-W, Wu J-C, Hunag K-L, et al: Traumatic brain injury in early childhood and risk of attention-deficit/hyperactivity disorder and autism spectrum disorder: a nationwide longitudinal study. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11857. From Taipei Veterans General Hospital, Taiwan; and other institutions. **Funded by Taipei Veterans General Hospital. The authors declared no competing interests.**

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## Youth Trauma and Early Adult Psychotic Experiences

Trauma during childhood or adolescence was associated with the occurrence of psychotic experiences in early adulthood, according to the results of a longitudinal study. The results support the idea that trauma has a causal relationship with psychotic experiences.

***Background:*** Research has suggested that childhood trauma is associated with increased risk of psychosis, but the causality of the association has remained unclear and few studies have compared the roles of different trauma types. Studies examining whether there is a critical period of risk have had inconsistent results. The present study was undertaken to clarify the effects of trauma type, developmental age, exposure frequency, and confounding variables on the association between childhood trauma and later psychotic experiences.

***Methods:*** The study was based on data from the Avon (U.K.) Longitudinal Study of Parents and Children. Members of the cohort were born in 1991–1992 and followed until 2017. Psychotic-like symptoms were assessed when cohort members were aged 12 years and again at 18 years, using the psychosis-like symptoms semi-structured interview. Children were asked whether they had any of 12 specific psychotic experiences (e.g., hallucinations, delusions, experiences of thought interference) during the previous 6 months. As 18-year-olds, they were questioned about onset of psychosis-like symptoms since age 12 years. Trauma variables were obtained from questionnaires completed by parents or self-reported by participants. The questionnaire items were grouped into 6 different trauma types (i.e., physical, sexual or emotional abuse, emotional neglect, domestic violence, bullying), and exposures were grouped by the age at which they occurred: early childhood (through age 4 years), middle childhood (5–10 years), and adolescence (11–17 years).

***Results:*** The sample consisted of 4433 individuals, 9.3% of whom were rated as having an actual or suspected psychotic experience by age 18 years. Of many potential confounding factors assessed, several were significant mediators of the relationship between trauma and psychotic experiences: gender, parental drug use, living in crowded conditions, low family income, and maternal education status. After adjustment for these factors, participants who had psychotic experiences were more frequently exposed to trauma than those with no psychosis. (See table.) No specific type of trauma was significantly more strongly associated than others with risk of a psychotic experience.

**Association Between Trauma Types and Later Psychotic Experiences**

| Trauma type | Proportion of patients affected | Adjusted odds ratio (OR)* in exposed patients± |
|---|---|---|
| Any | 64.5% | 2.91 |
| Physical abuse | 23.1% | 1.69 |
| Emotional abuse | 23.7% | 1.81 |
| Bullying | 32.9% | 2.05 |
| Sexual abuse | 11.0% | 2.50 |
| Domestic violence | 21.9% | 1.79 |
| Emotional neglect | 7.8% | 1.89 |

±All ORs are statistically significant ($p<0.001$).

Risk of psychotic experiences increased with the number of different types of trauma experienced, from 1 (OR, 1.94) to ≥3 (OR, 5.19). Exposure to trauma during any of the age periods was associated with risk, but the association was strongest for exposures during adolescence.

***Discussion:*** These results support a causal association between childhood trauma and later psychosis. Although the mechanism that underlies the association is unclear, it appears to be dependent on the severity, chronicity, and possibly recency of exposure.

Croft J, Heron J, Teufel C, Cannon M, et al: Association of trauma type, age of exposure, and frequency in childhood and adolescence with psychotic experiences in early adulthood. *JAMA Psychiatry* 2018; doi 10.1001\jamapsychiatry.2018.3155. From the University of Bristol, U.K.; and other institutions. **Funded by the U.K.'s Medical Research Council; and other sources. The authors declared no competing interests.**

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## Individualizing Methylphenidate

A wide array of modified-release methylphenidate products designed for once-daily dosing are now available, each characterized by a distinctive exposure time course. The previous standard of care, immediate-release (IR) methylphenidate, with its relatively short half-life requiring twice- or thrice-daily dosing, has been largely replaced by these newer agents. The modified-release agents differ in the proportion of immediate-release (IR) methylphenidate they contain and in their formulation technology. Their availability allows the prescriber to tailor daily methylphenidate exposure to each patient's needs, using such considerations as the length of the school day, homework load, domestic harmony, or an adult's workday demands.

Three key features distinguish the available modified-release methylphenidate products: the percentage of the dose formulated as IR, allowing for patient-specific needs in the rate of onset of action; early exposure, defined as the proportion of active ingredient released within the first 3 hours after administration; and the time to peak concentration ($T_{max}$), which is a surrogate for the duration of drug effects. (See table for an overview of pharmacokinetic data obtained from each product's FDA-approved labeling for healthy adults in a fasting state.)

| Current methylphenidate products | | | |
|---|---|---|---|
| **Common trade names** | **% IR** | **% released in 0–3 hours** | **$T_{max}$ (hours)** |
| **Short-acting (approximately 4 hours)** | | | |
| *Ritalin, Focalin* | 100% | 33–39% | 2–2.4 |
| **Intermediate-acting (approximately 6–8 hours)** | | | |
| *Metadate ER* | 0% | 17% | 4.1 |
| *Metadate CD, Quillichew ER, Quillivant XR, Cotempla XR-ODT* | 15–30% | 13–15% | 4–5 |
| **Long-acting (approximately 10–12 hours)** | | | |
| *Concerta* | 22% | 16% | 6 |
| *Aptensio* | 37% | 17% | 2–8 |
| *Ritalin LA* | 50% | 30% | 1.8/6.1± |
| *Focalin XR* | 50% | 21% | 1.5/6.5± |
| *Daytrana* (transdermal) | 0% | — | 10 |
| ±For low and high doses, respectively | | | |

Oral clearance of methylphenidate is lower, and pharmacokinetics are more variable in children. Food can delay $T_{max}$ values and may increase total exposure to the drug. In addition to the estimates in the table here, each product's labeling contains curves showing the unique exposure time course properties of each product, which can be matched with the individual needs of patients. Within products, the dose-proportional nature of methylphenidate activity can enable product-specific titration to an optimal maintenance dose.

In recent developments, following a large number of reports of reduced efficacy especially later in the day, 2 generic products have lost their "AB" designation as bioequivalent to OROS methylphenidate. They are now designated as "BX"—i.e., no longer substitutable for the innovator OROS methylphenidate (*Concerta*). A triple-layer dexmethylphenidate formulation, mimicking the old standard of practice of thrice-daily dosing, is in development. A recently approved evening-dose formulation (*Jornay PM*) is designed to delay the first pulse of drug release until 12 hours after ingestion, followed by extended release during the day. Also in the pipeline are a new prodrug form of methylphenidate with an even longer duration of action and other methylphenidate homologues with more specificity for target mechanisms and an even longer duration of action.

Patrick K, Radke J, Raymond J, Koller L, et al: Drug regimen individualization for attention-deficit/hyperactivity disorder: guidance for methylphenidate and dexmethylphenidate formulations. *Pharmacotherapy* 2018; doi 10.1002/phar.2190. From the Medical University of South Carolina, Charleston; and the University of Tennessee College of Pharmacy, Memphis. **Source of funding not stated. The authors declared no competing interests.**

## Sugar Consumption and ADHD

In a population-based cohort study, high sucrose consumption was associated with an increased prevalence of ADHD in 6-year-old boys. However, associations were not found in girls or with ADHD onset in later childhood.

***Methods:*** Subjects in this ongoing cohort study were enrolled at birth, in 2004 or later. The present analysis was based on evaluations when the children were aged 6 and 11 years. ADHD was identified in 6 and 11 year olds using the ADHD module of the Development and Well-Being Assessment, a 31-item parent questionnaire based on DSM criteria. At both evaluations, mothers or caregivers were administered a food frequency questionnaire with a 1-year recall. About 10 foods were identified as contributors of sucrose to the children's food intake, with sucrose content of foods estimated from USDA data. Sucrose consumption was divided into tertiles, and then combined to create 5 categories based on the pattern between the 2 evaluations: always low, always medium, always high, increasing, and decreasing.

***Results:*** The analysis included 3721 6 year olds, of whom 3497 also provided follow-up data at age 11 years. The mean sucrose consumption was higher in children with ADHD than in those without, at both ages 6 and 11. (See table). Because mean sucrose consumption differed significantly between boys and girls, the genders were analyzed separately. At age 6 years, after adjustment for multiple other factors, sucrose intake was significantly associated with ADHD in boys (1.8% in the lowest tertile, 2.8% in the middle, 5.8% in the highest; p=0.02). ADHD prevalence was not associated with sucrose consumption in 11-year-old boys or in girls at either age. The 5 different temporal patterns of sugar intake were not linked with ADHD onset between the ages of 6 and 11 in either boys or girls.

**Mean sucrose consumption (cross-sectional) in children with/without ADHD**

| | ADHD | No ADHD | Significance |
|---|---|---|---|
| **Age 6 years** | 131 g/day | 108 g/day | p=0.003 |
| **Age 11 years** | 187 g/day | 148 g/day | p<0.001 |

***Discussion:*** In this study population, sugar accounted for about 30% of all calories consumed by children, far above the World Health Organization's recommended 10% limit. An association between sucrose intake and ADHD is biologically plausible. However, it is also possible that higher sugar consumption in children with ADHD is a consequence of the disorder rather than a cause.

Del-Ponte B, Anselmi L, Assunção M, Tovo-Rodrigues L, et al: Sugar consumption and attention-deficit/hyperactivity disorder (ADHD): a birth cohort study. *Journal of Affective Disorders* 2019;243 (January):290–296. doi 10.1016/j.jad.2018.09.051. From the Federal University of Pelotas, Brazil; and other institutions. **Funded by the Brazilian Public Health Association; and other sources. The authors declared no competing interests.**

## Electronic Device Use and Psychological Distress

According to a series of national polls of U.S. adolescents, elevated use of electronic devices has a dose-related association with psychological distress. Although the study could not determine the causal direction of the association or whether it is reciprocal, it is likely due at least in part to the displacement hypothesis—i.e., elevated use of electronic devices deprives the individual of opportunities for constructive social or physical activity.

***Methods:*** The authors analyzed data from the national Youth Risk Behavior Survey, which samples representative groups of U.S. high-school students in biannual waves. This analysis was based on 5 waves of questionnaire data obtained between 2009 and 2017, with sample sizes of about 15,000 students per year. Elevated use was defined as use of a computer, smartphone, gaming device, or other electronic device for non-school-related purposes for ≥3 hours per weekday. The outcome variable, psychological distress, was a composite of 3 items: sadness or hopelessness leading to discontinuation of usual activities, serious suicidal ideation, and a suicide plan. To reduce selection bias, pairs of adolescents with and without elevated use were propensity score matched* on the basis of age, gender, race, body weight status, bullying victimization, smoking, alcohol use, physical activity, and insufficient sleep.

***Results:*** The prevalence of elevated electronics use increased from about 25% in 2009 to a plateau of 41% in 2013, probably reflecting market saturation of smartphones. Device use for ≥3 hours/day was more prevalent in boys until 2011, after which there was no difference between genders. The proportion of adolescents reporting ≥1 of the 3 mental health issues also increased, from 32% in 2009 to 36% in 2017 ($p<0.001$). During the last survey year, depression or sadness was present in 32% of adolescents, suicidal ideation in 17%, and a suicide plan in 14%. The proportion of adolescents with elevated electronic use was associated in a dose-related fashion with the number of mental health issues in each survey year ($p<0.001$).

***Discussion:*** Although it is possible that psychological distress drives increased screen time as a coping mechanism for low mood or loneliness, it is at least equally likely that excessive screen use negatively affects mood. In addition to the displacement hypothesis, the causal explanation may include sleep deprivation and cyberbullying.

Wang C, Li K, Kim M, Lee S, et al: Association between psychological distress and elevated use of electronic devices among U.S. adolescents: results from the youth risk behavior surveillance 2009-2017. *Addictive Behaviors* 201;90 (March):112–118. doi 10.1016/j.addbeh.2018.10.037. From Western Washington University, Bellingham; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

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**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

**Odds Ratio:** A comparison of the probability of an event. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio >1 indicates that the event is more likely to occur in that group than in the comparison 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.