

CHILD & ADOLESCENT PSYCHIATRY ALERTS

Amphetamine XR Suspension: Onset of Action	15
Cannabis Use and Adult Mental Health	17
Pharmacotherapies for Anxiety Disorders	16
Physical Aggression Trajectories.....	16
Reference Guide	18
Support Teams for Suicidal Adolescents	14
Trigeminal Nerve Stimulation for ADHD	13

Volume XXI / March 2019 / Number 3

www.alertpubs.com

[Interested in Self-Assessment CME? View our online activity catalog.](#)

Trigeminal Nerve Stimulation for ADHD

In a pilot, sham-controlled study, trigeminal nerve stimulation (TNS) resulted in symptomatic improvement in children with ADHD. TNS is currently approved in Canada and Europe for treatment of depression and epilepsy in adults and previously showed promising results in an open study in children with ADHD. The technique appears to be well tolerated and associated with minimal risks.

Methods: Participants, recruited from the community, were families with children, aged 8–12 years, who met DSM-5 criteria for ADHD of at least moderate severity based on standardized scales and clinical interview. Children were medication free for ≥ 1 month before the study. At the first clinic visit, families were taught how to place the TNS electrodes and operate the device. At night, the child wore a battery-operated stimulator, attached to the pajamas and by wire to 2 self-adhesive patch electrodes placed on opposite sides of the forehead. Double-blind active or sham stimulation was applied across the electrodes for about 8 hours every night. Children were evaluated in the clinic at baseline, weekly during 4 weeks of treatment, and then 1 week after discontinuation. The primary study outcome was the clinician-rated ADHD Rating Scale (ADHD-RS) total score.

Results: A total of 62 families were randomly assigned to treatment, and 59 completed the protocol. Withdrawals were not due to adverse effects. The mean patient age was 10 years, and the mean baseline ADHD-RS scores were 32 and 33 in the active and sham groups, respectively. During the first week, both the real and sham TNS groups experienced similar improvement in ADHD symptoms. However, during the remaining study weeks, improvement plateaued in the sham TNS group and continued, although at a slower rate, in the patients who received active TNS. Overall, TNS produced a larger decrease in ADHD-RS total score than sham treatment; ADHD-RS total scores at week 4 averaged about 24 in the active group, compared with 28 in the sham group (effect size, * 0.50). The effects of active TNS were comparable to those reported with nonstimulant ADHD medications. Improvements on both the inattentive and hyperactive/impulsive subscales of the ADHD-RS significantly favored active treatment. Clinical Global Impression scores reflected improvement at week 4 in 52% of patients receiving active treatment, compared with 14% of those receiving sham ($p=0.003$). Other measures of

CHILD & ADOLESCENT PSYCHIATRY ALERTS (ISSN 2640-8236) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: child@alertpubs.com. © 2019 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157 institutional. Subscribers may enroll in the 12-month CME program for an additional \$83.00 per year, or enroll in the comprehensive, annual Self-Assessment program for \$270 (in the U.S.). M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

behavior and sleep showed no between-group effects or nonsignificant effects. Patients who received active TNS showed EEG changes in right frontal and frontal midline regions when these were measured at the end of treatment. These changes were correlated with changes in ADHD-RS total and hyperactivity/impulsivity scores. ADHD-RS scores worsened in both groups between weeks 4 and 5, following treatment discontinuation.

There were no serious side effects of TNS reported. Compared with sham treatment, TNS was associated with weight gain, increased pulse, fatigue, headache, and increased appetite. These effects are not readily explained and require further investigation.

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

McGough J, Sturm A, Cowen J, Tung K, et al: Double-blind, sham-controlled, pilot study of trigeminal nerve stimulation for ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry* 2019; doi 10.1016/j.jaac.2018.11.013. From the University of California, Los Angeles; and other institutions including NeuroSigma, Inc., Los Angeles. **Funded by the NIMH. Three of 9 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Adult Support Teams for Suicidal Adolescents

The Youth-Nominated Support Team (YST), a psychoeducational social support intervention, was associated with reduced long-term mortality in adolescents hospitalized for suicidal ideation or suicide attempts.

Methods: Participants were adolescents, aged 13–17 years, hospitalized on a psychiatric unit with serious thoughts, a plan, or a recent attempt of suicide. The adolescents were randomly assigned to receive treatment as usual (TAU) with or without YST. Adolescents assigned to the YST intervention nominated a team of "caring adults" who were trained by the study staff to meet regularly with the adolescent after hospital discharge and provide support for treatment adherence and positive behavioral lifestyle choices. These adults were contacted weekly by study staff and encouraged to have weekly contact with the adolescents. The primary results of the trial (previously published) indicated a greater reduction in severity of suicidal thought at 6 weeks in YST participants, relative to those who received only TAU. The present analysis evaluated the long-term effects of YST participation over ≤ 14 years using data from the National Death Index.

Results: A total of 448 young people participated in the study. The mean age at entry was 16 years, and 71% of participants were female. The vast majority of patients (nearly 90%) had a diagnosis of major depressive disorder; other common diagnoses were disruptive behavior disorder, anxiety disorder, PTSD or acute stress disorder, and alcohol or substance use disorder. Adolescents in the YST group nominated a mean of 3.4 support persons, who were parents, grandparents, other family members, teachers, coaches, parents of friends, and youth-group leaders. These adults attended psychoeducation sessions lasting a mean of 1 hour and had a mean of nearly 10 contacts with the adolescent during the 3-month intervention. Young people who received YST also received more outpatient psychotherapy, medication follow-up, and drug treatment.

During long-term follow-up, there were 2 deaths in the YST group—a homicide and a suicide. A total of 13 patients who did not receive YST died during follow-up (hazard ratio,* 6.62); 8 of these deaths were due to suicide or drug abuse or overdose with unknown intent. When only the 9 drug-related and suicide deaths were considered, the hazard ratio increased to 8.2 ($p=0.02$). Although no longer statistically significant, potentially due to the very small number of occurrences, when only the 4 suicide deaths (4 in the TAU group, 1 in the YST group) were considered, the hazard ratio remained elevated at 3.05.

Discussion: Although YST was not associated with a statistically significant effect on suicides in this small group of patients, the study results indicate the intervention may be associated with positive youth trajectories and reduced mortality overall. In addition to the enhanced adherence to treatment plans shown in the primary results, adolescents who received YST may have benefited from an increase in perceived support and facilitation of problem solving and from skill development, furthered by communicating and accepting help from supportive adults.

King C, Arango A, Kramer A, Busby D, et al: Association of the youth-nominated support team intervention for suicidal adolescents with 11- to 14-year mortality outcomes: secondary analysis of a randomized trial. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2018.4358. From the University of Michigan, Ann Arbor. **Funded by NIMH. The authors declared no competing interests.**

*See Reference Guide.

Amphetamine XR Suspension Onset of Action

Results of a pilot study indicate that amphetamine extended-release oral suspension (AMPH EROS; *Dyanavel*) can produce positive effects as early as 30 min post dose in young patients with ADHD.¹

Background: AMPH EROS was approved in 2015 for treatment of ADHD, based on a placebo-controlled laboratory classroom study that showed an onset of action by 1 hour post dose, the earliest time point assessed.

Methods: Study subjects were 18 children, aged 6–12 years, with ADHD. AMPH EROS was initiated, and the dosage optimized over the first study week. After a practice laboratory classroom session, children were randomly assigned to receive AMPH EROS at a fixed dosage of 15, 17.5, or 20 mg/day or placebo in a randomized, crossover sequence for 2 additional classroom sessions, separated by 5 days. The onset of drug action was assessed as the change in score on the Swanson, Kotkin, Agler, M-Flynn, and Pelham Combined (SKAMP-C) rating scale from pre dose to 30 min post dose, relative to placebo.

Results: The study met its primary efficacy endpoint, with greater changes in the SKAMP-C score from pre dose to 30 min post dose with AMPH EROS, relative to placebo (6-point improvement, vs 2.5-point deterioration with placebo; effect size, * 0.95; $p < 0.0118$). AMPH EROS was also superior to placebo at 3 hours post dose (effect size, 1.57; $p = 0.0002$). Change in the Permanent Product Measure of Performance, a written math test and secondary study endpoint, did not differ between AMPH EROS and placebo at 30 min, but did differ at 3 hours. During the study, patients were exposed to medication for 11–13 days. Three children reported fatigue, 2 reported decreased appetite, and none experienced insomnia.

Discussion: The ideal action profile for an ADHD medication would be a single-dose agent with a rapid onset of action and an extended duration of effect, sustained into the early evening. Results of this study, although preliminary, support the suggestion of an early onset of action of AMPH EROS. Previous research has shown the agent has demonstrated efficacy for up to 13 hours post dose.²

¹Childress A, Kando J, King T, Pardo A, et al: Early-onset efficacy and safety pilot study of amphetamine extended-release oral suspension in the treatment of children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2019;29:2–8. doi 10.1089/cap.2018.0078. From the Center for Psychiatry and Behavioral Medicine, Inc., Las Vegas, NV; and Tris Pharma, Inc., Monmouth Junction, NJ. **Funded by Tris Pharma, Inc. All study authors disclosed potentially relevant financial relationships with commercial sources including Tris Pharma.**

²Childress A, 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. See *Child & Adolescent Psychiatry Alerts* 2018;20 (July):38–39.

*See Reference Guide.

Physical Aggression Trajectories

Results of a longitudinal cohort study suggest that developmental trajectories of physical aggression from early childhood to adolescence differ substantially between boys and girls. In addition, family characteristics measured when children were 5 months old were predictive of a high physical aggression trajectory in both boys and girls.

Methods: The Quebec Longitudinal Study of Child Development enrolled a representative population-based sample of children born in 1997 and 1998. The measure of physical aggression used throughout the study consisted of 3 behavioral items—engages in fights; physically attacks others; and hits, bites or kicks other children—rated from 1 (never) to 3 (often). Aggression was rated by an informant, nearly always the mother, in 7 interviews spanning the ages of 1.5 to 8 years; with teachers in 6 interviews from ages 6 to 13 years; and with the child at ages 10, 12, and 13 years. Children were included in the analysis if information was available from ≥ 10 of the 16 possible observations. Information on 12 family risk factors was obtained during the first interview with the mother, 5 months after the child's birth.

Results: The sample consisted of 2223 participants, of whom 91% were white and 51% were boys. As expected from previous research, overall physical aggression peaked around age 3.5 years and decreased substantially afterward until age 13 years. Rates were consistently lower in girls than in boys. However, the small percentage of boys (6%) with the highest levels of aggression demonstrated medium-to-increasing levels of parent-reported aggression from ages 1.5 to 8 years, followed by the highest levels of teacher- and self-rated aggression at ages 6–13 years. In contrast, 25% of girls fell in the category with the highest levels of physical aggression. The trajectory for these girls showed them as having the highest levels at all ages according to all informants. A number of parental and sociodemographic factors appeared to affect development of physical aggression. These included parental depression and education level; household income; mother's age at first childbirth; intact family structure; number of siblings at 5 and 17 months; and parental antisocial behavior during their own adolescence.

Discussion: Although it is well known that boys and girls differ in the use of physical aggression throughout development, most earlier published studies did not analyze the genders separately. The analysis of girls identified a group with a level of physical aggression that, although lower than that of boys, remained high throughout childhood and represented a large proportion of all girls. This group may be at high risk for problems with school achievement, nicotine use, early pregnancy, and intimate partner violence.

Teymoori A, Côté S, Jones B, Nagin D, et al: Risk factors associated with boys' and girls' developmental trajectories of physical aggression from early childhood through early adolescence. *JAMA Network Open* 2018; doi 10.1001/jamanetworkopen.2018.6364. From the University Medical Center Gottingen, Germany; and other institutions. **Funded by the Canadian Institutes of Health Research; and other sources. The authors declared no competing interests.**

Pharmacotherapies for Anxiety Disorders

Guidelines from the American Academy of Child and Adolescent Psychiatry recommend SSRIs and SNRIs as first-line medications for anxiety but note that other medications may also relieve anxiety. There are limited data that directly compare individual medications or drug classes specifically for pediatric anxiety. Results of a network meta-analysis* suggest sertraline may have the best balance of efficacy, tolerability, and safety.

Methods: A comprehensive literature search identified all randomized placebo-controlled trials, published between 1966 and 2017, evaluating any specific medication for treating anxiety disorders in patients aged <18 years and measuring the outcome with a validated rating scale. Trials in which patients received concurrent psychotherapy were excluded. Treatment response was the primary efficacy outcome of the analysis. Measurement scales were ranked in order of

preference, led by the Clinical Global Impression–Improvement scale, with a score of ≤ 2 , indicating response. Discontinuation was the primary measure of tolerability, and treatment-emergent suicidality was also assessed.

Results: The analysis included 20 published reports with data from 22 clinical trials in 2623 patients. The trials assessed 13 different medications (i.e., alprazolam; atomoxetine; buspirone; clomipramine; clonazepam; duloxetine; fluoxetine; fluvoxamine; guanfacine; imipramine; paroxetine; sertraline; venlafaxine) representing 6 medication classes. Most of the studies evaluated patients with mixed anxiety disorders, generalized anxiety disorder, social anxiety disorder, or school phobia.

Response rates with the $\alpha 2$ agonists, SSRIs, and SNRIs were significantly superior to placebo. In individual agent comparisons, fluvoxamine, sertraline, and fluoxetine were superior to placebo. Fluvoxamine was the most effective agent, and clomipramine was the least effective. Regarding the amount of symptomatic improvement, a secondary efficacy outcome, only SSRIs were more effective than placebo and paroxetine was the most effective single agent.

There were few differences in all-cause discontinuation among drugs or drug classes. Discontinuation due to adverse events occurred less often with SNRIs than with most other drug classes. Venlafaxine was the most tolerable active treatment; duloxetine and atomoxetine were also relatively well tolerated.

Treatment-emergent suicidality generally did not differ across medication classes; however, risk was elevated with benzodiazepines, relative to placebo. In pairwise comparisons, risk of treatment-emergent suicidality was greatest with paroxetine and lowest with sertraline. Five other agents—guanfacine, clonazepam, duloxetine, placebo, and venlafaxine—all had significantly greater risk of emergent suicide than sertraline.

Discussion: According to these results, SSRIs have greater efficacy than other medication classes in treating pediatric anxiety disorders, but at the cost of poorer tolerability than some other drug classes. Within the SSRI class, sertraline appears to have the optimal combination of efficacy and tolerability, while some other SSRIs (including paroxetine) are best considered second line. Although risk of treatment-emergent suicidality did not differ among medication classes, only benzodiazepines—which as a class do not carry a Black Box Warnings about suicidality in young patients—were associated with significantly greater risk than placebo.

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

Dobson E, Bloch M, Strawn J: Efficacy and tolerability of pharmacotherapy for pediatric anxiety disorders: a network meta-analysis. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.17r12064. From the University of Cincinnati College of Medicine, OH; and other institutions. **Funded by the NIMH. Two of 3 study authors declared potentially relevant financial relationships with industry sources.**

Common Drug Trade Names: alprazolam—*Xanax*; atomoxetine—*Strattera*; clonazepam—*Klonopin*; duloxetine—*Cymbalta*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; guanfacine—*Tenex*; imipramine—*Tofranil*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor*

*See Reference Guide.

Adolescent Cannabis Use and Adult Mental Health

According to the results of a meta-analysis, adolescents who use cannabis are more likely than those who do not to have onset of depression and anxiety in early adulthood. Rates of suicidal ideation and suicide attempts are also elevated in cannabis users.

Methods: A comprehensive review of the literature identified prospective longitudinal studies that controlled for the presence of depression and anxiety at baseline. The studies assessed cannabis use at least once when subjects were aged <18 years and again at least once between the ages of 18 and 32 years. Depression and anxiety were assessed using DSM criteria or other

standardized measures and compared between those who did and did not use cannabis. Outcomes were adjusted for multiple factors including age, gender, and depression and/or anxiety at baseline. Studies that could not be pooled for meta-analysis were included in a secondary systematic review.

Results: The meta-analysis included 11 studies, some reporting multiple outcomes. An additional 24 studies were identified and included only in the systematic review, primarily because of participant overlap or differences in how outcomes were reported.

Cannabis use in adolescence was associated with significantly increased risk of new-onset depression (odds ratio* [OR], 1.37). Risk was also slightly elevated for anxiety (OR, 1.18), but this did not reach statistical significance. Cannabis users also had significantly increased rates of suicidal ideation (OR, 1.5) and suicide attempts (OR, 3.46) in adolescence and young adulthood. Results of the systematic review generally supported the conclusions of the main analysis.

Although the overall association of cannabis use with depression did not vary according to age, younger users (aged 14 and 15 years) were at higher risk of suicidal behavior than older users. Risk was also higher in girls than in boys. Several studies found that stopping cannabis use before the end of adolescence did not protect young people from some of the negative outcomes. Other studies found cannabis use during adolescence and later depression and anxiety to be associated with academic unpreparedness, delinquency, and poor academic performance.

Discussion: Although the effect sizes are modest, they are important given the high prevalence of cannabis use by U.S. adolescents; about 20% of adolescents report cannabis use in the previous month, and 7% report daily or near-daily use. While the causality of the association could not be determined, these observations are consistent with brain-imaging studies showing neuroanatomic changes, mostly volume decreases, in young cannabis users.

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

Gobbi G, Atkin T, Zytynski T, et al: Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: a systematic review and meta-analysis. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2018.4500. From McGill University, Montreal, Canada; and other institutions. **Funded by the Canadian Institutes of Health Research; and other sources. Two of 11 study authors disclosed potentially relevant financial relationships; the remaining 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.

Network Meta-Analysis: Provides estimates of efficacy for multiple treatment regimens, even when direct comparisons are unavailable. This method extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common.

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.

Contributing Editors: **Kate Casano, MSHyg Bennett Silver, MD**

Consulting Editor: **Theodore A. Petti, MD**, Rutgers–Robert Wood Johnson Medical School

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann** Assistant Editor: **Donna Foehner**

Founding Editor: **Michael J. Powers**
