CHILD & ADOLESCENT PSYCHIATRY ALERTS

Bringing Clinical Research to Practice

Volume XXII / February 2020 / Number 2 www.alertpubs.com

Stimulants: No Increase in Cardiovascular Risk

A large U.S. claims-based study found no association between stimulants or atomoxetine (*Strattera*) and serious cardiovascular events in children with ADHD or autism spectrum disorder. Rates of these events were low and medications did not alter the risk.

Methods: Study data was collected from an administrative database including 184 million privately insured and 19 million Medicaid insured individuals covered between 2000 and 2016. Two cohorts were identified: children and adolescents (aged 3–18 years) with ADHD but not autism spectrum disorder and those with autism spectrum disorder with or without ADHD. Within each cohort, case patients were those who experienced a serious cardiovascular event: stroke, MI, or serious cardiac arrhythmia. For each case patient, 10 controls were identified, matched for age, sex, insurance type, and calendar time. Because the medications have a short duration of action, exposure was defined as current use versus non-use.

Results: The ADHD cohort, comprising >2.2 million patients, had 186 serious cardiovascular events over a mean of 2.66 years, for an incidence of 3.12 per 100,000 person-years. The autism cohort, with >326,000 individuals, had 48 events, for an incidence of 5.62 per 100,000 person-years; 9 of these patients also had ADHD. The most common event in both cohorts was stroke. ADHD medication was not associated with increased risk of serious cardiovascular events in either cohort. In the ADHD cohort, a serious cardiovascular event occurred in 34% of medicated patients and in 32% of controls (odds ratio,* 1.08). In the autism spectrum disorder cohort, rates were 12.5% and 22%, respectively (odds ratio, 0.49). Results were not modified by adjustment for covariates including underlying cardiovascular risk, comorbid medical and psychiatric illness, and concomitant medication use and did not vary for different medication dosages or for each of the 3 individual cardiovascular outcomes.

Discussion: Stimulants are associated with relatively minor increases in blood pressure, heart rate, and QT interval in children and adolescents, but the clinical outcomes are uncertain. The present study is consistent with most previous evidence, which showed little if any increase in risk for cardiovascular events. The study adds a sufficient sample size to confidently rule out an association, more up-to-date data than most previous studies, and a separate examination of risk in children with autism spectrum disorders, who may also be exposed to psychotropic drugs. The rate of serious cardiovascular events in this study population was low. However,

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. 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 $93.00 per year, or enroll in the comprehensive, annual Self-Assessment program for $280 (in the U.S.). M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

the authors point out that case patients were more likely to have underlying cardiac conditions than controls, which suggests that warnings about using these drugs in vulnerable individuals may not always be followed.

Houghton R, de Vries F, Loss G: Psychostimulants and serious cardiovascular events in children with ADHD or autism spectrum disorder. *CNS Drugs* 2020;34:93–101. From F. Hoffman-La Roche Ltd., Basel, Switzerland ; and Maastricht University Medical Center, Maastricht, the Netherlands. **Funded by F. Hoffman-La Roche. Two of 3 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

***See Reference Guide.**

Stepped Treatment for ADHD and Aggression

In a controlled trial of children with ADHD and aggressive behavior not fully responsive to optimized stimulants and behavioral therapy, adjunctive treatment with risperidone or divalproex reduced aggressive behavior. Risperidone was more effective than divalproex but was associated with weight gain.

Methods: The study enrolled children, aged 6–12 years, with ADHD and either oppositional defiant disorder or conduct disorder. Aggressive behavior, measured using the parent-completed Retrospective-Modified Overt Aggression Scale (R-MOAS), was required to be clinically significant for the preceding week, and participants were required to have recent or current stimulant treatment. At study entry, all medication was discontinued and open-label stimulant titration was carried out to identify the child's most effective and best tolerated regimen. All families received weekly behavioral-oriented psychosocial treatment throughout the study. Children whose aggressive behavior persisted and who achieved some benefit from stimulants were randomly assigned to receive double-blind, flexibly-dosed adjunctive treatment with divalproex, risperidone, or placebo for 8 weeks. The primary outcome was change from baseline in aggressive behavior, measured with the R-MOAS. Remission was defined as a R-MOAS score of <15.

Results: Of 175 children who began study treatment, 151 (86%) completed the stimulant titration phase, 96 (64%) of whom fulfilled the criteria for remission of aggressive behavior, with subthreshold R-MOAS scores for 3 consecutive weeks. A total of 42 children did not achieve remission and were treated with randomly assigned medication. The mean duration of the stimulant optimization phase was 66.5 days in children whose aggression remitted and 75.4 days in those who went on to randomized treatment.

At the end of 8 weeks, the mean risperidone dose was 1.15 mg/day (range, 0.5–3 mg/day) and the mean valproic acid dose was 713 mg/day (range, 250–1750 mg/day; mean serum level, 77.75 ml/L). At the end of study treatment both groups receiving active medication demonstrated further improvement in aggression, although the degree of improvement remained less than in those who achieved remission with stimulant monotherapy. The difference from placebo was larger in the risperidone group (effect size,* 1.3; $p<0.003$) than in the divalproex group (effect size, 0.9; $p<0.046$). Secondary outcomes—scores on the Child Behavior Checklist for Aggressive Behavior and Rulebreaking Behavior—showed a similar pattern. Remission of aggression was achieved by 69% of the risperidone group, compared with 40% of the divalproexgroup and 37% of the placebo group ($p=0.023$). No serious adverse events were reported duringthe study. Neutropenia developed 1 risperidone-treated patient and a widespread skin rash developed in 1 divalproex-treated patient. Both reactions resolved with medication discontinuation. However, children in the risperidone group gained more weight during the 8 weeks oftreatment than those who received divalproex: 8 lbs vs 1.5 lbs.

Discussion: The present findings confirm the beneficial effects of risperidone and divalproex on aggression that is refractory to first-line stimulant and behavioral treatments. However, despite improvement, patients who received adjunctive treatment remained more symptomatic than

those who remitted with stimulant monotherapy, reinforcing the need to optimize first-line stimulant therapy. Although effective, given their adverse effect liability, adjunctive medications should be used as sparingly as possible.

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

Blader J, Pliszka S, Kafantaris V, et al: Stepped treatment for attention-deficit/hyperactivity disorder and aggressive behavior: a randomized, controlled trial of adjunctive risperidone, divalproex sodium, or placebo after stimulant medication optimization. *Journal of the American Academy of Child and Adolescent Psychiatry* 2020; doi 10.1016/jaac.2019.12.009. From the University of Texas Health Science Center, San Antonio; and other institutions. **Funded by the NIMH; and the National Center for Research Resources. Two of 12 study authors disclosed potentially relevant financial relationships with pharmaceutical-industry sources.**

Common Drug Trade Names*: divalproex—*Depakote*; risperidone—*Risperdal

***See Reference Guide.**

Lisdexamfetamine in Preschoolers

A multicenter open-label study of lisdexamfetamine (*Vyvanse*) in preschool-aged children with ADHD found safety, tolerability, and efficacy similar to that reported in older children. Lisdexamfetamine is currently approved only for use by patients ≥6 years.

Background: Although there are no medications approved to treat ADHD in preschool children and limited evidence exists for efficacy and safety in this population, a recent claims review indicated that almost 40% of these children receive psychostimulant treatment. The present FDA-requested study was conducted to obtain preliminary safety, tolerability, pharmacokinetic, and clinical response data for lisdexamfetamine in preschool-aged children with ADHD.

Methods: Children aged 4–5 years who had a confirmed diagnosis of ADHD and scores above a clinical cutoff on the ADHD-Rating Scale-IV Preschool version (ADHD-RS-IV-PS) were eligible for study participation provided they participated in a structured group activity (e.g., preschool, sports) that allowed for evaluation of symptoms and impairment outside of their home. Participants were also required to have undergone an adequate course of pharmacological or nonpharmacological treatment or to have symptoms severe enough to warrant medication without prior treatment. Following a ≤28-day screening and washout period, the 24 participants underwent a 6-week dose-optimization, a subsequent 2-week maintenance phase, and a 1-week safety follow-up. Lisdexamfetamine was initiated at 5 mg/day and increased weekly to a maximum of 30 mg/day. Individual patient's optimal dose was defined as that which produced a ≥30% reduction in ADHD-RS-IV-PS score and a Clinical Global Impression Improvement rating of at least much improved with acceptable safety and tolerability.

Results: Of the 24 patients enrolled, 19 completed the study. Most participants were male (75%) and had the combined ADHD subtype (88%). Baseline severity was marked in nearly half of the children, and the mean ADHD-RS-IV-PS score was 44 (range, 32–51). The optimized lisdexamfetamine dose was 30 mg/day in 9 children, 20 mg/day in 2 children, 15 mg/day in 6 children, and 10 mg/day in 2 children. An optimal dose was not reached by the 5 children who discontinued study participation.

Nearly 80% of children experienced an adverse effect, but none were considered serious/severe or resulted in death. Similar to older patients, the most commonly reported adverse effects were decreased appetite (33%) and insomnia (17%). Vital sign changes were variable, but generally comprised small increases in diastolic blood pressure (mean, 1.5 mmHg) and decreases in systolic blood pressure (mean, -1.1 mmHg), pulse (mean, -0.8 bpm) and weight (mean, -0.9 lbs). Pharmacokinetics in study subjects were also similar to those in older children, with lisdexamfetamine peak concentrations reached at about 1 hour post-dose and

d-amphetamine peak concentrations about 2–6 hours post-dose. Steady-state clearance was not affected by dose, weight, or age. The decrease in ADHD-RS-IV-PS score at week 8 was 26 points, and 83% of children were rated as much or very much improved.

Discussion: Although the efficacy results are limited by the small sample, short trial duration, and lack of a placebo comparator, they are in line with those reported for older children and adolescents treated with lisdexamfetamine. Tolerability also appears to be similar, and no new safety signals emerged.

Childress A, Findling R, Wu J, et al: Lisdexamfetamine dimesylate for preschool children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2020;30 (3); doi 10.1089/cap.2019.0117. From the Center for Psychiatry and Behavioral Medicine, Las Vegas, NV; and other institutions. **Funded by Shire. All study authors disclosed potentially relevant financial relationships.**

Family Therapy for PTSD/Substance Problems

In adolescents with comorbid PTSD and substance use problems, an integrative therapy for both problems was as effective as standard therapy at reducing PTSD symptoms. Contrary to common expectation, the exposure-based feature of the treatment did not worsen substance use and was associated with reduced long-term use of illicit drugs and alcohol.

Background: Integrative therapy risk reduction through family therapy (RRFT) is an amalgam of cognitive-behavioral interventions for PTSD, multisystemic therapy for substance use, and sexual health interventions. It is currently the only integrated treatment for adolescents with co-occurring PTSD and substance use problems that has a supportive evidence base. In an effort to reduce PTSD-related substance use, the therapy includes gradual exposure to address PTSD symptoms by developing narratives of traumatic events to extinguish distress symptoms arising from trauma cues. Therapy is provided in a variable number of weekly individual sessions, with brief caregiver and family sessions when needed.

Methods: The present study initially enrolled patients aged 13–18 years, with ≥5 PTSD symptoms and a history of sexual abuse. Later the criteria were broadened to include young people who had suffered other types of interpersonal violence. Substance use problems were defined as ≥1 nontobacco substance-using day in the prior 90 days. Patients were randomly assigned to RRFT or to treatment as usual, the latter provided by a different group of therapists and consisting of whatever treatment they would typically implement in this situation—most often trauma-focused CBT. The primary study outcomes were the number of substance-using days and PTSD symptom severity at 3, 6, 12, and 18 months.

Results: The trial enrolled 124 adolescents (mean age, 15 years; 87% girls): 74% reported alcohol use, 70% marijuana use, and 13% use of other substances. The average number of experienced forms of trauma was 3.6. Mean treatment length was 18.5 sessions for RRFT and 12.5 sessions for treatment-as-usual. About 72% of RRFT patients and 65.5% of controls completed treatment.

At baseline, the average number of days with any substance use during the previous 3 months was 14.5. Both treatment groups showed marked decreases in substance use from baseline to 12 months, eventually averaging fewer than 2–3 days of self-reported exposure in the previous 3 months. At 18 months, substance use remained at this low level in the RRFT group but increased in the control group, although not to baseline levels. At 18 months, patients receiving RRFT had lower rates of alcohol, marijuana, and polysubstance use than controls. PTSD symptoms improved to a similar extent in both treatment groups, as did the symptom domains of re-experiencing, avoidance, and hyperarousal.

Discussion: Treatment decisions in this patient population are often guided by concern that exposure-based treatment may exacerbate substance use. The present results suggest that the

treatment is safe and does not increase substance use. However, the positive results require replication in larger samples that include a greater proportion of boys.

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

Danielson C, Adams Z, McCart M, et al: Safety and efficacy of exposure-based risk reduction through family therapy for co-occurring substance use problems and posttraumatic stress disorder symptoms among adolescents. A randomized clinical trial. *JAMA Psychiatry* 2020; doi 10.1001/jamapsychiatry.2019.4803. From the Medical University of South Carolina, Charleston; and other institutions. **Funded by the National Institute on Drug Abuse. The authors declared no relevant financial relationships with commercial sources.**

***See Reference Guide.**

Guideline for Sleep Problems in Autism

Children and adolescents with autism spectrum disorder and sleep disturbances often receive combined medication, behavioral therapy, and complementary and alternative treatments, including melatonin. Despite a high prevalence of sleep abnormalities in this population, an extensive literature search conducted by a guideline development committee of the American Academy of Neurology identified little evidence regarding treatment. Melatonin, the only intervention found to be superior to placebo, was recommended with low-to-moderate confidence.

The guideline committee reviewed the effects of treatment on bedtime resistance, sleep onset latency, sleep continuity, total sleep time, and daytime behavior in 8 articles that met quality criteria for inclusion in the evidence review. The studies evaluated melatonin, with or without CBT, parent-based sleep education, weighted blankets, and sound-to-sleep (STS) vibrating mattress technology.

The recommendations call for evaluating and addressing coexisting medical illnesses and medications that may contribute to sleep disturbance. Behavioral strategies, although not evidence-supported, should be tried before medication. These strategies may include imposing regular bed and wake-up times, progressively lengthening the time parents ignore bedtime resistance, calming rituals, and bedtime fading (i.e., putting the child to bed close to the time the child begins to fall asleep). Family-based CBT is another first-line approach. When other strategies fail, melatonin may be tried. However, it should be noted that the reviewed studies all used pharmaceutical-grade melatonin, and over-the-counter preparations have variable concentrations of the active substance and their effects may differ. Immediate-release melatonin may be more helpful for sleep-onset insomnia and controlled-release forms for sleep maintenance. Adverse effects of melatonin include morning drowsiness, increased enuresis, dizziness, diarrhea, rash, and hypothermia. Long-term safety in children has not been investigated. Finally, parents are often interested in complementary/alternative approaches. Of these, only STS mattresses and weighted blankets have been studied, showing little or no evidence of efficacy.

Buckley A, Hirtz D, Oskoui M, et al: Practice guideline: treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology* 2020;94 (March 3):1–13. doi 10.1212/WNL.0000000000009033. From the NIMH; and other institutions. **Funded by the American Academy of Neurology. Seven of 26 study authors disclosed potentially relevant financial relationships with pharmaceutical-industry sources.**

Transitioning to Adult Mental Health Services

The transition from child and adolescent mental health services (CAMHS) to adult services (AMHS) can be problematic and the process is often negative for youth and their caregivers. Although the aim of transitioning is to ensure continuity of care, up to 60% of youth stop accessing mental health services during or after the transition. A recent literature review found very few interventions have been developed to guide the transition and none are standardized. However, several core actions were identified that could facilitate successful transitions.

Transition policies. Integrated care pathways and a transition policy/statement that describe the steps involved in transition process should be developed. Transition plans should be individualized based on patient and caregiver input, developmentally appropriate, and agreed upon by both CAMHS and AMHS. Protocols should include standards for communication, information sharing, and record-keeping. Roles for all individuals should be clearly defined and all staff should have the knowledge, skills, and training to support the policies. Finally, a process should be created to assess and evaluate the transition protocol.

Transition tracking and monitoring. A process for identifying youth who will be transitioning to adult services (e.g., flow sheet, log book) and to track those who have made the transition should be developed. Ideally patients should be identified ≥6 months before the transition date.

Transition readiness. Transition readiness assessments should be conducted with the youth and their caregiver(s) regularly to identify needs and goals. Patients and caregivers should be educated about differences in CAMHS and AMHS programs.

Transition planning. In addition to the patient, caregiver, and both CAMH and AMHS providers, other individuals (e.g., primary care providers, school representatives) may be involved in the transition planning process. The individualized transition plan, which may include results of readiness assessments, goals, medical summaries, and emergency care plans, should be shared with all parties. Communication with the primary care provider is essential to ensure they have accurate medication and treatment information. Eligibility criteria for adult programs should be reviewed and confirmed to avoid a lapse in care, and the optimal timing of transfer of care should be determined. The youth and their caregiver(s) should be provided with information for self-care resources, community supports, and community mental health resources that can be contacted if the patient withdraws from AMHS services.

Transfer of care. Patients should only be transferred to AMHS if they are clinically stable. A meeting or case conference that includes all parties (i.e., youth, caregivers, CAMHS and AMHS clinicians) should be held to officially hand off care. Documentation of the transfer including referral letters, the transition plan, and medical records) should be sent to all involved parties.

Transfer completion. CAMH clinicians should contact the patient 3–6 months after their last visit to confirm transfer to AMHS and offer consultation assistance if needed.

Cleverley K, Rowland E, Bennett K, et al: Identifying core components and indicators of successful transitions from child to adult mental health services: a scoping review. *European Child & Adolescent Psychiatry* 2020; 29:107–121. From The University of Toronto, Canada; and other institutions. **The review was conducted with no external funding. 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.

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 is based on a reports from Agency for Healthcare Research and Quality (AHRQ). Checklists are posted at alertpubs.com.

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