

CHILD & ADOLESCENT PSYCHIATRY ALERTS

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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):17102240. 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 anti-psychotic 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 $\geq 50\%$ 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.

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

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

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 D₁ 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 D₂ 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 D₁ receptor has an excitatory function in the circuits that underlie these types of movement, and the D₂ receptor has an inhibitory function. Theoretically, blocking either pathway should reduce hyperkinetic movements. D₂ 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 D₁ 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.

¹Gilbert 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.**

²Gilbert 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.

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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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