CHILD & ADOLESCENT PSYCHIATRY ALERTS

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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.**

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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

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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 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.

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