

CHILD & ADOLESCENT PSYCHIATRY ALERTS

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Long-Term Methylphenidate

According to the results of placebo-controlled withdrawal study, extended-release methylphenidate continues to benefit children and adolescents after 2 years of use, although the overall effect is modest. The study results support guideline recommendations to assess periodically whether patients, particularly adolescents, should continue treatment.

Methods: Study participants, recruited from 2 clinics in the Netherlands, were aged 8–18 years and had been taking methylphenidate in any dosage or form for ≥ 2 years. During the 4 weeks before the study, regardless of previous formulation and dose, all patients received 36 or 54 mg/day extended-release methylphenidate, whichever was closer to their pre-study dosage. At baseline, participants were randomly assigned to continue taking methylphenidate or to a 3-week taper followed by placebo treatment. Concomitant medications and psychotherapies were continued without change. The primary outcome was change in clinician-rated ADHD DSM-5 Rating Scale (ADHD-RS) score at 7 weeks. Secondary outcomes included the Conners' Teacher Rating Scale–Revised (CTRS) and the Clinical Global Impression–Improvement (CGI-I) scale.

Results: A total of 94 patients (mean age, 14 years) were enrolled. Half were switched to extended release methylphenidate before study entry, and the mean duration of treatment was 4.5 years. A total of 11 patients in the withdrawal group and 3 in the continuation group withdrew from the study before week 7 because of worsening behavioral function (23% vs 6%; $p=0.049$).

Baseline ADHD-RS scores averaged about 20 points and deteriorated to a greater degree in the discontinuation group than in those who continued methylphenidate (5 points vs 0.5 points; $p=0.006$; effect size,* 0.23). The difference was largely due to scores on the inattention subscale. Withdrawing methylphenidate was associated with poorer results in patients below the median age but not in older adolescents. CGI–Improvement scores indicated worsening in 19 patients in the placebo group and in 7 who continued receiving methylphenidate (40% vs 16%; number needed to treat* to avoid one patient's worsening, 4). CTRS ratings, showed

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greater deterioration in the discontinuation group (6.6 point between-group difference; $p < 0.05$; effect size, 0.52). Differences in teacher ratings were largely due to worsening hyperactivity rather than inattention.

Discussion: The small effect size for methylphenidate continuation, compared with those found in acute treatment studies, could suggest that the drug may become less effective when used over a longer period. However, the benefits of continuation may be underestimated in the present study in part because many eligible patients declined to participate because they felt methylphenidate was still working well for them. Furthermore, the sample may have over-represented patients in whom the effects of methylphenidate were less pronounced, perhaps because of milder ADHD symptoms or ADHD that was resolving. The CGI results indicate that while a majority of patients were continuing to benefit from methylphenidate, many could be discontinued from the drug without deterioration.

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

Matthijssen A, Dietrich A, Bierens M, Deters R, et al: Continued benefits of methylphenidate in ADHD after 2 years in clinical practice: a randomized placebo-controlled discontinuation study. *American Journal of Psychiatry* 2019;176 (September):754–762. doi 10.1176/appi.ajp.2019.18111296. From the University of Groningen, the Netherlands; and other institutions. **Funded by the Netherlands Organization for Health Research and Development. Two of 8 study authors disclosed potentially relevant financial relationships.**

Common Drug Trade Names: methylphenidate, extended-release—*Concerta, Ritalin LA*

*See Reference Guide.

Amantadine for DMDD

A 12-year-old girl with a history of complex trauma and a diagnosis of disruptive mood dysregulation disorder was admitted to an inpatient unit with severe aggression and suicidal and homicidal ideation. Multiple previous medication trials had been unsuccessful and she had been hospitalized on several previous occasions. The patient's family history was notable for schizophrenia, autism spectrum disorder, anxiety disorder, and a suicide attempt. In addition, she had experienced major stressors including sexual abuse and neglect. Her current medication regimen, which included aripiprazole, oxcarbazepine, buspirone, and prazosin, produced only modest effects on DMDD and PTSD symptoms. Substantial weight gain led to obesity, which decreased her self-esteem and created negative peer interactions.

On admission, metformin was added to decrease metabolic risks, and aripiprazole was cross-tapered with amantadine, which was titrated to 200 mg b.i.d. The patient deteriorated during the cross-taper, and risperidone was added to control agitation. She also received individual, group, and milieu therapy during and after the medication adjustments. Over the subsequent 2 weeks, her behavior significantly improved and risperidone was discontinued without worsening of behavioral control. The patient was discharged receiving 200 mg amantadine b.i.d., 600 mg oxcarbazepine b.i.d., 15 mg buspirone t.i.d., and 2 mg/day prazosin. At 1-year follow-up she remained stable with outpatient treatment.

Prefrontal lobe underactivity is believed to be a primary contributor to the chronic irritability present in young patients with DMDD. Chronic stress and complex trauma may also contribute to neurotransmitter dysregulation. Amantadine may restore prefrontally-mediated inhibitory function via N-methyl-d aspartate (NMDA) blockade, facilitation of presynaptic dopamine release, and antagonism of postsynaptic dopamine reuptake.

Rice T, Simon H, Barckak D, Maiyuran H, et al: Amantadine for treatment of disruptive mood dysregulation disorder symptoms. *Journal of Child and Adolescent Psychopharmacology* 2019; 29 (8):642–646. From Ichan School of Medicine at Mount Sinai, New York, N.Y.; and other institutions. **One of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: amantadine—*Symmetrel*; aripiprazole—*Abilify*; buspirone—*BuSpar*; metformin—*Glucophage*; oxcarbazepine—*Trileptal*; prazosin—*Minipress*; risperidone—*Risperdal*

Social Media and Mental Health

In a prospective study of adolescents, social media use was associated with increased risk of internalizing and combined internalizing/externalizing problems. Social media use was not associated with externalizing problems alone.

Methods: The Population Assessment of Tobacco and Health (PATH) study consists of a representative sample of U.S. adolescents aged 12–17 years. The present analysis was based on data from 3 consecutive annual waves of the study. In wave 1, participants, aged 12–16 years, contributed data on lifetime emotional problems and other relevant factors such as age, sex, and marijuana and alcohol use. Adolescents were questioned about their time spent using social media during wave 2 (ages 13–16 years). In wave 3 (ages 14–17 years), participants completed the Global Appraisal of Individual Needs—Short Screener, a screening test for probable mental health disorders, with subscales for externalizing and internalizing symptoms. Population-attributable fractions* were calculated to estimate the number of high-symptom cases that could be prevented by reducing social media use.

Results: The sample consisted of 6595 adolescents who contributed data at each of the 3 waves. During wave 3, 9% of the sample reported internalizing problems alone, 14% described externalizing problems alone, 18% reported both problem types, and 59% were free of these problems. Social media use was associated with all 3 problem categories, but the association with externalizing problems did not persist after adjustment for wave 1 factors. Both internalizing and comorbid problems showed a dose-related association with social media use. (See table.) Contrary to some previous studies, associations between social media use and mental health problems were not influenced by participants' sex. Based on the adjusted model and assuming no confounding, up to 19% of internalizing problems and up to 15% of externalizing problems could have been prevented if adolescents had spent less time using social media.

Associations of time spent on social media with internalizing and externalizing problems ^a		
Time spent on social media per day (wave 2)	Adjusted relative risk ^a	
	Internalizing problem alone	Comorbid internalizing and externalizing problems
>30 min to ≤3 hours (n=2000)	—	1.59
>3 to ≤6 hours (n=817)	1.60	2.01
>6 hours (n=571)	1.78	2.44

^aCompared with no social media use and adjusted for wave 1 variables

Discussion: Several mechanisms could account for the association between social media use and internalizing problems. High users of social media may experience poorer quality sleep, be subject to cyberbullying, be exposed to unfavorable comparisons with others, or lack face-to-face social interactions. Future research should determine whether setting limits on the time spent on social media or redesigning social platforms could reduce mental health problems in young people.

Riehm K, Feder K, Tormohlen K, Crum R, et al: Associations between time spent using social media and internalizing and externalizing problems among US youth. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2019.2325. From Johns Hopkins University, Baltimore, MD; and other institutions. **Funded by the NIMH; and other sources. Two of 9 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Atomoxetine-Associated Raynaud's Phenomenon

A 7-year-old boy with autism spectrum disorder presented with hyperactivity, impulsivity, and aggressive behavior indicative of ADHD. He was started on 10 mg/day atomoxetine (*Strattera*) that was titrated over 3 weeks to 28 mg/day. Within 1 hour of the first 28-mg dose, bilateral digital pallor, cooling, and circumoral cyanosis developed. The symptoms persisted for 2 days before being reported to the patient's physician. On examination, all other physical and laboratory evaluations were unremarkable, and no underlying cause for the cyanosis was identified. He received a diagnosis of Raynaud's phenomenon, which is often associated with stress, cold exposure, or autoimmune disorders, but has been reported less frequently as a medication-associated reaction. Atomoxetine was discontinued and the symptoms resolved.

Raynaud's phenomenon is a rare adverse effect—only 1 previous case has been reported with atomoxetine—and the pathophysiology is unclear. However, it may be related to vasoconstriction in peripheral vessels resulting from atomoxetine-associated increases in norepinephrine and dopamine.

Nur Gulle Z, Karayagmurlu A, Coskun M: Raynaud's phenomenon related with atomoxetine treatment in a child with autism and attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2019; doi 10.1089/cap.2019.0025. From Istanbul University, Turkey. **The authors declared no competing interests.**

Evening Dosed Methylphenidate

In a pivotal clinical trial in children with ADHD, the delayed extended-release formulation of methylphenidate (*Jornay PM*), designed to be administered in the evening in order to control early morning ADHD symptoms, was superior to placebo at improving functional performance over a 12-hour laboratory classroom day.

Methods: Study participants were children, aged 6–12 years, with a diagnosis of ADHD who were either currently receiving methylphenidate or who had previously shown response to the agent with acceptable tolerability. Individual patient dosing was optimized during the first 6 study weeks, when participants received 1 of 5 available doses of study medication, ranging from 20 to 100 mg/day. During these weeks an optimal administration time of between 6:30 and 9:30 PM was also established. Following 2 weeks of optimized treatment, participants were randomly assigned to continue methylphenidate or were switched to placebo for 1 week. At the end of the week, children were assessed during 9 sessions in the laboratory classroom. The primary study endpoint was the average of all classroom assessments on the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale, a 13-item scale of observer-rated behavior.

Results: The multicenter trial enrolled 161 participants. A study site was removed from the analysis because of a randomization error and 6 patients were withdrawn from the study before randomization. The final analysis was based on 117 patients. The mean optimized methylphenidate dose was 66 mg/day and the mean optimal time of administration was 8 PM.

During the open-label treatment phase, patients demonstrated marked improvements in ADHD symptoms, behavior, and early morning functioning. Mean scores on the ADHD Rating Scale IV, the Before School Functioning Questionnaire, and the Conners Global Index-Parent scale were all improved by $\geq 74\%$. Adverse events were consistent with other methylphenidate formulations.

During the laboratory classroom day, children who received the study drug had significantly lower SKAMP combined scores than the placebo group (14.8 vs 20.7). Analyses including and excluding the questionable study sight had similar results. When individual time points were analyzed, active treatment was significantly superior to placebo at 7 of the 9 time points (all but

8 AM and 8 PM). Classroom performance, as measured with the Permanent Product Measure of Performance, showed a similar pattern of improvement throughout the day. Early morning functioning, measured using the morning subscale of the Parent Rating of Evening and Morning Behavior-Revised, was also significantly better with active treatment.

Discussion: This trial focused primarily on functional improvement, using rating scales appropriate for evaluating performance by different observers throughout the waking day. The unexpected lack of statistical difference between the active drug and placebo at 8 AM may have been due to relatively good control of behavior in the placebo group.

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

Childress A, Cutler A, Marraffino A, McDonnell M, et al: A randomized, double-blind, placebo-controlled study of HLD200, a delayed-release and extended-release methylphenidate, in children with attention-deficit/hyperactivity disorder: an evaluation of safety and efficacy throughout the day and across settings. *Journal of Child and Adolescent Psychopharmacology* 2019; doi 10.1089/cap.2019.0070. From the Center for Psychiatry and Behavioral Medicine, Inc., Las Vegas, NV; and other institutions. **Funded by Ironshore Pharmaceuticals and Development Inc. All 10 study authors disclosed potentially relevant financial relationships, including 9 with Ironshore.**

*See Reference Guide.

Obesity Treatment and Depression/Anxiety

According to the results of a meta-analysis, participation in a structured obesity treatment program has positive effects on psychological well-being in children and adolescents. However, a small proportion of participants may be at risk for worsening psychopathology and may require additional support.

Background: Young people with obesity are at increased risk of developing depression and anxiety. However, spontaneous dieting during adolescence is associated with high levels of depression, leading to concerns about emotional effects of obesity treatment programs, particularly those that employ dietary restriction.

Methods: A comprehensive literature review identified studies of children and adolescents, aged ≤ 18 years, treated for overweight or obesity. For inclusion in the meta-analysis, treatment programs had to include a dietary component and could not include online interventions, pharmacotherapy, or bariatric surgery. Studies were required to report on symptoms of depression or anxiety at baseline and postintervention or follow-up using a validated instrument.

Results: A total of 44 studies, comprising >3000 participants, met inclusion criteria. Mean baseline body mass index ranged from 25 to 45 and mean patient age ranged from 6 to 17 years. The studies used specific calorie restrictions or calorie deficits or diets based on local guidelines, the Traffic Light Diet, or restriction or promotion of specific foods. Other interventions included physical activity education, supervised exercise programs, behavior modification strategies, and cognitive-behavioral therapy or dialectical behavior therapy.

Patients who received structured treatment experienced a small but significant average decrease in depressive symptoms (standard mean difference, $* 0.31$; $p < 0.001$), which was maintained for up to 16-months of follow-up. Higher body mass index at baseline was associated with a larger decrease in depression. Improvements were largest in studies conducted in a tertiary setting, those with weekly or less frequent contact, and studies providing nutritional education rather than an energy prescription. Interventions without a physical activity component did not reduce depressive symptoms. Results regarding anxiety improvements were mixed, with 8 of 13 studies reporting positive effects. Overall, the effect on anxiety was small to medium and statistically significant (standardized mean difference, 0.38 ; $p < 0.001$). Studies providing structured exercise classes had the greatest

positive effect on anxiety. There were no association between weight-related outcomes and changes in depression or anxiety. A few of the studies reported worsening of symptoms in a small number of participants.

Discussion: Participation in obesity treatment, particularly during adolescence, may interrupt the trajectory of depressive symptoms. The negative effects of spontaneous dieting in adolescents do not appear to carry over to professionally run interventions.

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

Jebeile H, Gow M, Baur L, Garnett S, et al: Association of pediatric obesity treatment, including a dietary component, with change in depression and anxiety: a systematic review and meta-analysis. *JAMA Pediatrics* 2019; doi 10.1001/jamapediatrics.2019.2841. From the University of Sydney, Australia; and other institutions. **Funded by the University of Sydney; and other sources. The study authors declared no industry-related financial relationships.**

*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.

Number Needed to Treat (NNT): 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.

Population Attributable Fraction: The proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario (e.g. no tobacco use).

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.

Standardized Mean Difference: The difference between two normalized means - i.e. the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales, a value of 0–0.2 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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