CHILD & ADOLESCENT PSYCHIATRY ALERTS

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Psychosis Risk: Methylphenidate Vs Amphetamine

According to pooled data from 2 large healthcare claims databases, risk of psychosis in adolescents and young adults with ADHD is substantially higher after starting treatment with amphetamine than with methylphenidate.[1] Although new-onset psychotic episodes are uncommon, the risk difference may be clinically important given the widespread use of the drugs.

Background: The FDA requires manufacturers of stimulants to include a warning regarding treatment-emergent psychosis or mania in product labeling. Both amphetamine and methylphenidate influence dopamine. While amphetamine increases dopamine release to a greater extent, methylphenidate more potently inhibits dopamine transporters, which is believed to be a less important mechanism in causing psychosis.

Methods: Data was collected from 2 large U.S. claims databases with national coverage and a combined total of >250 million patients. Subjects were included in the analysis if they were aged 13–25 years, had a diagnosis of ADHD, and were newly prescribed amphetamine or methylphenidate between 2004 and mid-2015. Follow-up began 7 days after the initial prescription, and the primary study outcome was a new inpatient or outpatient diagnosis of psychosis, accompanied within 60 days by a prescription for an antipsychotic medication. Cases of psychosis were reviewed and confirmed by a study psychiatrist.

Results: Propensity score-matching* for a broad range of sociodemographic and psychiatric characteristics in the amphetamine and methylphenidate groups resulted in a total cohort of nearly 222,000 patients. During follow-up, there were 343 episodes of psychosis, 106 in the methylphenidate group and 237 in the amphetamine group (1.78 vs. 2.83 per thousand person-years). The median time from drug dispensation to the psychotic episode was 128 days. Risk for psychosis was significantly higher in the amphetamine group (hazard ratio,* 1.65). However, the risk difference was evident only in patients treated by family physicians or internists, not by psychiatrists. Relative risk with amphetamines was larger in younger patients than those aged ≥18 years and in those who received extended-release rather than immediate-release formulations.

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Editorial:[2] While observational studies can provide information on uncommon adverse events in real-world settings, they cannot establish causality. Thus, whether the emergent psychosis was due to stimulant use, to an inherent vulnerability, or to a combination of these factors is unknown. The lack of a difference in risk when patients were treated by a psychiatrists may suggest that prodromal psychotic features that could increase the risk of treatment-related psychosis were more readily identified by psychiatrists who then avoided prescribing amphetamine for those patients. Although the management of stimulant-associated psychosis was not addressed, analysis of FDA data indicates that for the vast majority of patients (92%) psychotic symptoms resolve after discontinuation of the stimulant even without antipsychotic medication.

[1]Moran L, Ongur D, Hsu J, Castro V, et al: Psychosis with methylphenidate or amphetamine in patients with ADHD. *NEJM* 2019;380 (March 21):1128–1138. doi 10.1056/NEJMoa1813751. From Brigham and Women's Hospital, Boston, MA; and other institutions. **Funded by the NIMH. Four of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Cortese S: Psychosis during attention deficit–hyperactivity disorder treatment with stimulants [editorial]. *NEJM* 2019;380 (March 21):1178–1180. doi 10.1056/NEJMe1900502. From the University of Southampton; and Solent NHS Trust, U.K. **The author declared no competing interests.**

***See Reference Guide.**

Lithium Maintenance in Bipolar Disorder

Results of a multicenter, placebo-controlled discontinuation trial in children and adolescents support the use of lithium as maintenance treatment in bipolar I disorder.

Methods: Study participants, aged 7–17 years, were enrolled in the discontinuation trial after meeting response criteria in either of 2 clinical trials of open-label lithium, 1 of which also included a placebo-controlled phase. Response was defined as a Young Mania Rating Scale (YMRS) score of <10 and a Children's Depression Rating Scale–Revised (CDRS-R) score of <35 with stable therapeutic lithium levels. During the 28-week randomized discontinuation phase, lithium dosage was maintained by unblinded clinicians using recommended trough levels between 0.8 and 1.2 mEq/L. In the placebo group, lithium was withdrawn incrementally over the initial 4 weeks. Patients were permitted to receive psychotherapy during postacute open-label treatment and the discontinuation trial. Other medications were permitted to treat residual symptoms of psychosis, mania/hypomania, depression, anxiety, and ADHD. The primary outcome of the trial was treatment withdrawal for any reason. Treatment could be discontinued at the physician's discretion, for onset of persistent moderate symptoms of depression or mania based on the CDRS-R or YMRS, or for persistent worsening on the Clinical Global Impression–Improvement scale.

Results: The trial included a total of 31 patients, with a mean age of 12 years. Of these, 13 patients completed all 28 weeks of the discontinuation trial without recurrence of mood symptoms: 11 of 17 in the lithium group and 2 of 14 in the placebo group (65% vs 14%; hazard ratio* for discontinuation, 0.28; p=0.015). Of the 5 patients who discontinued during lithium treatment, 3 did so because of manic symptoms and 2 for mixed symptoms. In the placebo group, 5 patients had recurrence of manic symptoms and 5 others mixed symptoms. Patients in the lithium group completed a mean of 21 weeks of treatment, compared with 9 weeks in the placebo group (p=0.043).

Adverse events were common in both study groups but generally mild to moderate in severity. Lithium was stopped in 1 patient who developed moderate aggression that was considered possibly related to study treatment. Increased suicidal ideation was not reported as an adverse event. Lithium treatment was not associated with weight gain or metabolic abnormalities.

Discussion: This study adds to the extremely limited data on long-term treatment of bipolar I disorder in young patients. The small sample size is consistent with the difficulty of enrolling and maintaining such patients in long-term outpatient studies.

Findling R, McNamara N, Pavuluri M, Frazier J, et al: Lithium for the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled discontinuation study. *Journal of the American Academy of Child and Adolescent Psychiatry* 2019;58 (February):287–296. doi 10.1016/j.jaac.2018.07.901. From Johns Hopkins University, Baltimore, MD; and other institutions. **Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Eight of 17 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Methylphenidate and Academic Performance

According to a meta-analysis summarizing >3 decades of research, methylphenidate has small-to-medium positive effects on math accuracy and academic productivity in elementary-school children with ADHD. The analysis is the first to determine that the drug improves academic accuracy, not just speed.

Methods: The analysis included English-language studies evaluating the effects of immediate- or extended-release or transdermal methylphenidate on academic functioning in samples consisting primarily or exclusively of children with ADHD. The studies were required to evaluate in a crossover or parallel-group design the effects of methylphenidate versus placebo on standardized achievement tests for math, reading, or spelling. Math and reading tests were always conducted within a fixed time period.

Results: The meta-analysis included 34 studies with a total of 1777 participants. An additional 7 studies (425 children) were included in a qualitative synthesis. Most of the studies (88%) used a placebo controlled crossover design, and in three-fourths, the methylphenidate dosage was titrated for symptom control before the children were tested.

On math tests, children taking methylphenidate had high productivity—i.e., they attempted more questions—and also had greater accuracy. (See table.) In reading, methylphenidate was associated with more questions attempted, but not with greater accuracy. There were too few studies of spelling for this outcome to be included in the meta-analysis. However, methylphenidate was associated with improved spelling in 1 of 3 studies.

Effects of methylphenidate on academic performance in elementary-school children with ADHD

Test	Number of studies	Number of subjects tested	Effect size*	Significance
Math accuracy	29	1528	0.03	p=0.001
Math productivity	17	912	0.078	p<0.001
Reading accuracy	9	207	0.062	p=NS
Reading questions attempted	5	100	0.47	p<0.001

There was little evidence of publication bias, except possibly for the studies of reading accuracy. The analysis considered many potential mediators or moderators of the effect of methylphenidate on performance, including ADHD symptom severity and improvements, age, gender, ADHD subtype, and methylphenidate formulation and dosage. None of these factors influenced outcomes. No differences were found between immediate- and extended-release methylphenidate in academic performance improvement.

Discussion: These results reinforce the contrast between the large ADHD symptom improvements observed with methylphenidate and the modest improvements in academic performance, which are limited to certain academic subjects and are small or absent for measures of accuracy. Whether these observed effects may eventually result in better school performance long term has not been investigated.

Kortekaas-Rijlaarsdam A, Luman M, Sonuga-Barke E, Oosterlaan J: Does methylphenidate improve academic performance? A systematic review and meta-analysis. *European Child & Adolescent Psychiatry* 2019;28:155–164. doi 10.1007/s00787-018-1106-3. From the University of Amsterdam, the Netherlands; and King's College London, U.K.
Source of funding not stated. Two of 4 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.

***See Reference Guide.**

Inpatient Dialectical Behavior Therapy and Suicide

According to the results of an observational study, dialectical behavior therapy (DBT) may reduce incidence of suicide attempts, self-injury, and aggression in hospitalized adolescents. In addition to the clinical benefits, the results indicate that resource use may also be reduced.

Methods: Participants, aged 12–17 years, were admitted to a private, coeducational, acute care unit because of imminent safety concerns that could not be addressed outside the hospital. Admissions could be voluntary or involuntary and occurred during the 8 months following implementation of DBT on the inpatient unit. Outcomes in these patients were compared with historical controls—patients hospitalized on the same unit during the corresponding 8 months of the previous year. Patients received DBT milieu treatment adapted for adolescents, which included coaching, a token economy including a protocol for egregious behavior, resources such as handouts and homework, and artwork that conveyed DBT themes. All patients participated in 9 DBT skills groups per week, additional therapeutic and leisure groups, and individual and family psychotherapy. The historical control group received cognitive behavior therapy, intensive psychotherapy, and other interventions. Outcomes compared between the 2 groups included suicide attempt; non-suicidal self-injury; patient-to-patient aggression; patient-to-staff aggression; constant observations hours for indications of suicide, self-injurious behavior, and aggression; and use of restraints or seclusions. A cost savings analysis was conducted to evaluate the cost impact of reduced hours of constant observation.

Results: A total of 425 patients were admitted during the study period and were hospitalized for a mean of 8 days. The 376 patients admitted during the comparison period were hospitalized for a mean of 11 days. About 80% of patients had an affective disorder as their primary diagnosis.

Compared with controls, patients in the DBT group had fewer mean hours of constant observation for suicidal ideation (2.37 vs 10.55 hours), self-injury (0.72 vs 6.19 hours) and aggression (1.15 vs 3.89 hours); only self-injury was statistically significant (p=0.01). Although uncommon, patients who received DBT had fewer suicide attempts (p=0.01) and incidents of self-injury (p=0.04) and less use of restraints (p=0.01). Significant differences were not observed for incidents of aggression towards other patients or staff, seclusions, or readmissions.

The cost analysis showed a savings of >$250,000 on staff time for constant observation during implementation of DBT, compared with treatment as usual. About half of the cost savings were attributed to less observation for suicidal ideation, and the rest due to less observation for aggression and self-injurious behaviors.

Discussion: The authors note that treatment during the control period was quite robust and included several components that were carried over to the DBT period, such as a token economy and intensive individual and family therapy. It is likely that the 2 programs had

similar intensity. Although patients who received DBT did not have significantly fewer number of constant observation hours for suicidal ideation or aggression, seclusions, aggressive incidents, or readmissions, and effect sizes were small, descriptive statistics did show decreases in all of these outcomes.

Tebbett-Mock A, Saito E, McGee M, Woloszyn P, et al: Efficacy of dialectical behavioral therapy versus treatment as usual for acute-care inpatient adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* 2019; doi 10.1016/j.jaac.2019.01.020. From Zucker Hillside Hospital, Glen Oaks, NY. **Source of funding not stated. The authors declared no competing interests.**

Infections Linked With Eating Disorders in Girls

Adolescent girls with a history of severe or frequent infections are at increased risk of eating disorders, according to the results of a Danish cohort study. This finding supports the suspected involvement of inflammatory or autoimmune processes in the development of eating disorders.

Methods: Study data was collected from universal central healthcare and research registries in Denmark, and was limited to girls because the incidence of eating disorders in boys is low. Subjects were girls born between 1989 and 2006 and followed until the end of 2012. The analyses included 2 exposures of interest: hospitalization for infection before the onset of an eating disorder and the number of filled outpatient prescriptions for an anti-infective agent, an indicator of less severe infections. Because most people are prescribed an anti-infective at some point, the investigators used a cutoff of ≥3 prescriptions to define exposure. The study outcome was a first inpatient, outpatient, or emergency contact for an eating disorder. Each eating disorder diagnosis was analyzed separately.

Results: The study population consisted of >500,000 girls who were followed to a mean age of 16 years. The incidence per 100,000 person-years was 46 for anorexia nervosa, 15.2 for bulimia and 38.8 for eating disorder NOS. Risk of each type of eating disorder was increased in girls who had a history of hospitalization and in those with frequent outpatient anti-infective prescriptions. (See table.) A dose-response association was observed for each eating disorder, with hazard ratios* increasing according to the number of hospitalizations or prescriptions. For each disorder, the incidence was highest in the first 3 months after hospitalization or since the last redeemed prescription. However, several of the associations with dose or temporality were not retained in a sensitivity analysis limited to girls born after 1995, who had complete information on prescriptions since birth (the database was less complete before 1995).

Adjusted hazard ratios for eating disorders based on treated infections±

	Anorexia nervosa (n=2131)	Bulimia (n=711)	Eating disorder NOS (n=1398)
Hospitalization for infections (any vs none)	1.22	1.35	1.39
Anti-infective prescriptions (≥3 vs < 3)	1.23	1.63	1.45

±Adjusted for age, calendar period, parental education, and parental psychiatric history

Discussion: These observations confirm the results of earlier studies conducted in smaller populations. Contrary to the earlier findings, this study showed an association between infection and all 3 eating disorder diagnoses. Risk estimates are of a similar magnitude to those

reported for infections in schizophrenia, mood disorders, and nonaffective psychosis. In relation to eating disorders, infections and inflammation have been observed to trigger fevers, loss of appetite, and decreased food intake, changes that could increase the risk of a full-blown eating disorder in susceptible persons. Infections could also affect mood and behavior via effects on the gut-brain axis.

Breithaupt L, Köhler-Forsberg O, Larsen J, Benros M, et al: Association of exposure to infections in childhood with risk of eating disorders in adolescent girls. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2019.0297. From George Mason University, Fairfax, VA; and other institutions. **Funded by the Swedish Research Council; and other sources. One of 7 study authors disclosed a potentially relevant financial relationship; the remaining 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.

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.

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.