CHILD & ADOLESCENT PSYCHIATRY ALERTS

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Update on Pediatric Antidepressant Use

A systematic review of pediatric depression trials conducted in the last decade suggests that the evidence continues to support escitalopram and fluoxetine as first-line treatment and that the risk of emerging suicidality may be lower than previously suggested.[1]

Background: A comprehensive meta-analysis of pediatric antidepressant use, published in 2007, found the agents have small positive effects on depression in children and adolescents.[2] Another review, which factored the potential for suicidality in a risk/benefit profile, found no advantage for any 1 antidepressant agent over others.[3] The present systematic review was undertaken to reevaluate the previous findings based on controlled trials conducted within the last decade, which made use of newer rating scales such as the Columbia Suicide Severity Rating Scale that provides a more detailed view than adverse-event data.

Methods: The updated review was based on 7 pediatric clinical trials of antidepressant treatment for major depressive disorder that were conducted after the 2007 meta-analysis. Studies of treatment-resistant and bipolar depression were excluded, as were those in patients whose depression was comorbid with any other major psychiatric disorder (i.e., ADHD, substance use). Of the 7 trials, 4 evaluated acute-phase treatment, 3 extension-phase treatment, and 2 relapse prevention.

Results: The 4 acute-phase trials evaluated fixed- and flexible-dose duloxetine, transdermal selegiline, and escitalopram. Response rates with duloxetine and selegiline were similar to those with placebo, and the trials were regarded as inconclusive as a result of high placebo response rates. The escitalopram trial showed superior efficacy of active treatment versus placebo as acute treatment, with a response rate of 64% for escitalopram and 53% for placebo (p=0.003; effect size,* 0.27).

The 2 duloxetine studies included 26-week extension periods, during which fluoxetine—the active control in both studies—was also extended. Rates of remission did not differ between duloxetine and fluoxetine in the 2 studies. The escitalopram study was also extended for 16–26 weeks, and patients who continued receiving open-label escitalopram had significantly higher rates of remission than the placebo group (51% vs 36%; p=0.002).

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Maintenance treatment with fluoxetine and sertraline was evaluated in single continuation trials. Fluoxetine was found to be significantly superior to placebo for relapse prevention, with an odds ratio* for relapse of 3.2 in the placebo group. Adolescents receiving sertraline relapsed at a lower rate than their respective placebo group, but the results did not reach statistical significance, possibly because of a small sample size and a high dropout rate.

Of the 4 acute-phase trials, 3 assessed suicidality using the Columbia Suicide Severity Rating Scale. Regardless of the measure, there were no differences in rates of suicidal events between active medication and placebo in any of the acute-treatment studies. However, rates were higher in the studies that used the Columbia Scale (about 5–10%) than in the study that considered only adverse event reports (about 3%). While rates of suicidality increased in the extension studies, there continued to be no significant between-group differences. The relapse-prevention trials evaluated suicidality as a self-reported adverse effect leading to medication discontinuation. These found higher rates of suicidality with placebo than with fluoxetine (4% vs 2%) and no reported suicidality with either placebo or active treatment in the sertraline trial.

Discussion: The acute-phase and extension trials were conducted by pharmaceutical companies at multiple sites, ranging from 26 to 65, while the 2 relapse-prevention trials were publicly funded (by the NIMH and the Canadian Institutes of Health Research) and carried out at 1 and 3 sites, respectively. This may be important because the industry-sponsored studies may have been flawed by recruitment pressures, leading to enrollment of some patients with subthreshold depression, and by inexperience of clinicians at some low-volume sites. A high number of study sites is known to contribute to a high placebo response rate. Differences between active drug and placebo are typically larger in NIMH-funded than industry-funded studies, owing to a lower rate of placebo response.

Study Rating*—16 (89%): This study met most criteria for a systematic review, but the source of funding was not disclosed.

[1]Ignaszewski M, Waslick B: Update on randomized placebo-controlled trials in the past decade for treatment of major depressive disorder in child and adolescent patients: a systematic review. *Journal of Child and Adolescent Psychopharmacology* 2018;28:668–675. doi 10.1089/cap.2017.0174. From Boston Children's Hospital, MA; and other institutions. **Source of funding not stated. One study author disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

[2]Bridge J, et al.: Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA* 2007;297:1683–1696.

[3]Cipriani A, et al: Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 2016;388:881–890.

Common Drug Trade Names*: duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; selegiline transdermal—*Emsam*; sertraline—*Zoloft

***See Reference Guide.**

Antipsychotics and Unexpected Death

In a retrospective cohort study, antipsychotic use, primarily for off-label indications, was associated with increased risk of unexpected death in young patients.[1] Risk was significantly elevated in patients who received higher-dose therapy.

Methods: Study data were collected from the Tennessee Medicaid program for patients aged 5–24 years who were given a prescription for an antipsychotic or a control psychiatric medication (i.e., ADHD medications, antidepressants, mood stabilizers). Patients were excluded from the analysis if they had a life-threatening somatic illness, if they had a diagnosis of schizophrenia or related psychoses, or a neurologic indication for an antipsychotic. Patients were followed for ≤5 years after their index prescription or until age 25 years, but person-time was counted only during periods of exposure to the drug. Antipsychotic dosage was stratified with a cutoff of 50 mg chlorpromazine equivalents, the approximate median in this sample. Deaths were counted if they occurred outside the hospital or within 7 days after hospital admission.

Results: The study cohort included nearly 60,000 new users of an antipsychotic, about evenly divided between higher and lower doses, and nearly 190,000 users of control medications. The majority of patients in the lower-dose antipsychotic group (66%) received risperidone, while those in the higher-dose group most commonly received quetiapine (34%), aripiprazole (23%), or olanzapine (17%). Half of the control-group patients received antidepressant therapy, and 43% received ADHD medications.

There were 67 deaths in the control group, about two-thirds attributable to injuries and suicide. There were 8 deaths in the lower-dose antipsychotic group, not significantly different from the control group; but 40 deaths in the higher-dose antipsychotic group (146 per 100,000 person-years vs 55 per 100,000 person-years in controls; $p<0.001$). After adjustment for a large number of covariates (e.g., demographic characteristics, concurrent psychoactive medications, comorbid psychiatric and somatic illness), compared with the control group, the overall hazard ratio [HR]* for death in patients receiving higher-dose antipsychotic therapy was 1.8. The difference was primarily attributable to an increased incidence of unexpected death (HR, 3.51), not death from injury or suicide (HR, 1.03). The higher-dose group had an increased risk of death from cardiovascular or metabolic causes (HR, 4.29). There was a modest, nonsignificant increase in deaths from unintentional drug overdose in the higher-dose group.

Discussion: Unexpected deaths should be rare in a young population without serious somatic illness. The present findings support existing guidelines to restrict prescribing to limited indications, try alternative treatments first, carry out cardiometabolic assessment and monitoring, and restrict therapy to the lowest possible dose and shortest possible duration.

Editorial.[2] This investigation did not find the increase in unexpected death to be attributable to suicide. However, some deaths may have been undetected suicides, possibly by overdoses with coprescribed drugs or with illicit drugs that are not routinely assayed. This may be particularly likely in the patients who received high doses of antipsychotics who also had high rates of mood disorders, ADHD, conduct disorders, and impulsivity, all of which are risk factors for suicide. In addition, patients with schizophrenia and Tourette syndrome were excluded from the study population because antipsychotics are the only medication option for these diagnoses while the studied disorders have alternative treatment possibilities. Studying the association of antipsychotics with unexpected death may be especially important because nonantipsychotic medication options for these patients are limited. Research to confirm and extend the present findings should include cases from across the diagnostic spectrum and a large enough sample to determine the effects of specific antipsychotics, doses, and drug combinations on unexpected death.

[1]Ray W, Stein M, Murray K, Fuchs C, et al: Association of antipsychotic treatment with risk of unexpected death among children and youths. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.3421. From Vanderbilt University School of Medicine, Nashville, TN; and other institutions. **Funded by National Heart, Lung, and Blood Institute; and the National Institute for Child Health and Human Development. The authors declared no competing interests.**

[2]Geller B: Antipsychotics, excess deaths, and paradoxes of child psychiatry [editorial]. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.3409. From Washington University, St Louis, MO. **The author declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal

***See Reference Guide.**

Infections and Neuropsychiatric Disease Risk

In a Danish nationwide cohort study, infections were associated with increased risk of mental disorders during childhood and adolescence. This study extends previous research that showed associations for a narrower range of infections and psychiatric outcomes.

Methods: The study cohort consisted of all children born in Denmark between 1995 and mid-2012. Using linked registry data, the investigators identified all hospitalizations for infections and all filled prescriptions for anti-infective agents. Study outcomes were all inpatient and outpatient diagnoses of a mental disorder (excluding substance abuse and organic mental disorders) and all prescriptions for antipsychotics, anxiolytics, antidepressants, ADHD medications, and drugs for substance dependence. Because the association between infections and mental illness might be influenced by genetic or shared environmental factors, a separate analysis was conducted using siblings of children with infections as a comparison group.

Results: The cohort consisted of nearly 1.1-million individuals, who had a mean age of 10 years at last follow-up (range, 1–18 years). About 4% were hospitalized for a mental disorder, and 5.2% received a prescription for a psychotropic medication. Risk of neuropsychiatric disorders was increased in those with a history of hospitalization for an infection or treatment with an anti-infective agent. (See table.) Risk was elevated to a similar degree for bacterial, viral, and other infections and for all types of antibiotics, with similar hazard ratios for broad-, moderate-, narrow-spectrum, and topical agents. Risk was also elevated, although not statistically significantly, for antivirals and antimycotics, but not for antiparasitic drugs. Risks were increased across all age groups, with no clear group at greater vulnerability.

Risk of any treated mental disorder according to history of hospitalization for infection or prescription of an anti-infective agent

	Hazard Ratio*	
	Hospitalization for mental disorder	**Prescription for psychotropic medication**
Hospitalization for infection†	1.84	1.42
Treatment with anti-infective agents††	1.40	1.22
Treatment with antibiotics	1.41	1.22

†Reference group = no hospitalizations for infection
††Reference group = no anti-infective medication

Incidence of a mental illness was highest in the 3 months immediately following the infection and remained elevated for up to 10 years. Risks increased in a dose-dependent manner with the number of infections. Associations were found for multiple categories of mental illness, but risk was particularly pronounced for OCD, schizophrenia spectrum disorders, personality and behavior disorders, mental retardation, autism spectrum disorders, ADHD, oppositional-defiant and conduct disorders, and tic disorders. In the sibling analysis, children hospitalized or treated for an infection had higher rates of mental illness than their siblings.

Discussion: This appears to be the most detailed analysis to date of the association between treated infections from birth to late adolescence and the risk of mental disorders. The finding that risks were still present but attenuated in the sibling analysis suggests familial influences may also contribute to the development of mental illness. Pathogenic mechanisms that may explain the relationship include direct effects of infection on the brain, inflammatory or autoimmune processes, or effects of anti-infective medication on the gut microbiome.

Kohler-Forsberg O, Petersen L, Gasse C, Mortensen P, et al: A nationwide study in Denmark of the association between treated infections and the subsequent risk of treated mental disorders in children and adolescents. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.3428. From Aarhus University Hospital, Risskov, Denmark; and other institutions. **Funded by the Lundbeck Foundation; and the Independent Research Fund Denmark. The authors declared no competing interests.**

***See Reference Guide.**

Childhood Seizures and Risk of Psychiatric Disorders

According to results of a Danish population-based cohort study, individuals who experience febrile seizures or epilepsy during early childhood are at increased risk for mental illness during adolescence and early adulthood.

Methods: The study cohort consisted of all persons born in Denmark between 1978 and 2002 and surviving to at least age 10 years. Children were categorized into 4 groups: those who received a diagnosis of epilepsy before age 10 years; those who experienced febrile seizures between the ages of 3 months and 5 years in the absence of preexisting epilepsy; those who experienced both types of seizure; and those who experienced no seizures. Information on psychiatric diagnoses that typically develop during adolescence or early adulthood was obtained from a registry covering all admissions to psychiatric hospitals, emergency rooms, or outpatient clinics. The childhood-onset disorders ADHD and autism were not considered in the analysis.

Results: The cohort consisted of nearly 1.3 million children, of whom 3% had febrile seizures, 1% had a history of epilepsy, and <1% had experienced both. The cohort was followed to a mean age of 21 years, by which time 6% had received a psychiatric diagnosis. Compared with children who experienced no seizures, those with febrile seizures had a modest increase in risk (hazard ratio [HR],* 1.12) and those with epilepsy (HR, 1.34) or both seizure types (HR, 1.50) had larger risk elevations. The excess risk was present across a range of disorders, with the strongest association for schizophrenia in children with any seizure history. Similar, although less pronounced, excess risk was present for mood disorders and anxiety and stress-related disorders. Children with both seizure types generally had the highest risk for all disorders, although in view of the small number of children in this group, risk estimates were relatively imprecise. Associations compounded with an increasing number of admissions for febrile seizures and for later onset of childhood epilepsy.

Discussion: Many studies in clinical samples have reported an association of childhood seizures with psychiatric illness, but there have been few other large-scale studies investigating the full range of outcomes. The association with febrile seizures is a novel finding, perhaps because febrile seizures have been studied less frequently, as they are considered benign. The causal relationship between seizures and mental illnesses is unclear. Seizures or their treatment may harm the developing brain, or the seizures and psychiatric disorders may have common underlying causal factors.

Dreier J, Pedersen C, Cotsapas C, Christensen J: Childhood seizures and risk of psychiatric disorders in adolescence and early adulthood: a Danish nationwide cohort study. *Lancet Child and Adolescent Health* 2018; doi 10.1016/s2352-4642(18)30351-1. From the National Center for Register-Based Research, Aarhus, Denmark; and other institutions. **Funded by the Novo Nordisk Foundation; and other sources. Three of 4 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

***See Reference Guide.**

ADHD Genetic Risk Loci Identified

A meta-analysis of genome-wide association studies (GWAS) has for the first time identified risk loci for ADHD. Previous studies showed that ADHD risk is highly heritable, but this meta-analysis, due to its large sample size, was able to newly identify specific risk loci. The results also support previous evidence that ADHD represents the extreme end of a continuum of symptoms or traits.

Twin studies have suggested that the heritability of ADHD is 70–80% throughout the lifespan. Earlier genome-wide studies have lacked the sample size and statistical power to identify

DNA variants that contribute to risk. The present analysis was conducted using GWAS data from 12 cohorts that included >20,000 persons with ADHD and >35,000 controls. A total of 304 genetic variants in 12 different loci with statistically significant associations with ADHD were identified. While compelling, these 12 loci likely capture only a small fraction of genetic risk for ADHD. Selection and evolutionary pressures may also be features of the genetics of ADHD. The study also found ADHD risk variants to be strongly enriched in genomic regions conserved in mammals, and constrained genes likely to be intolerant to loss-of-function mutations are associated with ADHD.

ADHD risk was also found to be associated with other traits or trait groups including several types of cancer; intelligence and educational attainment; major depressive disorder; anorexia; multiple aspects of obesity; metabolic traits such as type 2 diabetes; smoking; insomnia; and mortality. These correlations confirm previous research suggesting overlap between several psychiatric syndromes. The correlation with health risk behaviors such as smoking and obesity also confirms previous observations and may reflect an impaired ability to self-regulate and inhibit impulsive behavior.

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

Demontis D, Walters R, Martin J, Mattheisen M, et al: Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nature Genetics* 2018; doi 10.1038/s41588-018-0269-7. From the Lundbeck Foundation, Aarhus, Denmark; and other institutions. **Funded by the Lundbeck Foundation; and other sources. Several study authors disclosed potentially relevant financial relationships.**

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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.

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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