Neural and Genetic Correlates of ADHD

Over the past 2 decades, substantial research using new technologies has been focused on investigating neurologic and genetic associations of ADHD. New brain-imaging approaches have led to the description of alterations in brain anatomy and circuitry associated with the disorder. In genetics, endophenotypes (distinct heritable traits that reflect genetic influences more closely than the disorder itself) are an expanding focus of research. Which of these neural and genetic associations are causal, rather than adaptations to the disorder, remains to be established. Development of new interventions and preventive strategies will rely on identifying pathways of causation from genes to neural circuits to behavior.

Neuroimaging studies have implicated several large-scale neural circuits in ADHD, particularly those related to sustained attention, inhibitory control, motivation, and emotional regulation. Structural MRI studies have consistently identified volumetric reductions in the basal ganglia, which are important to goal-directed behaviors, motivation/reward processing, and motor control—all impaired in persons with ADHD. These alterations lessen as the individual develops and are no longer detectable by adulthood, suggesting that ADHD may be a disorder of delayed maturation. Structural MRI has also identified abnormalities in frontal and parietotemporal cortical thickness in ADHD. Delays in reaching peak cortical thickness in children with ADHD also support the hypothesis of delayed maturation.

Connectivity analyses have been carried out using data from diffusion MRI (dMRI) and from testing of both resting-state and task-based functional connectivity. dMRI studies have identified deficits in white matter organization in dorsal frontostriatal and frontoparietal circuits and mesocorticolimbic circuits that might be related to deficits in motivation. These findings complement structural MRI studies in that the affected white matter tracts connect regions with volumetric abnormalities. Resting state functional connectivity studies have identified reduced connectivity within the default mode network (DMN), which may underlie self-referential cognitions, introspection, and mind-wandering. Persons with ADHD may have difficulty deactivating the DMN when turning to tasks that require attention. The DMN normally works in
opposition to the cognitive control network, which is involved in executive functions. However, persons with ADHD may lack the normal inverse correlation between activity of these 2 networks. Task-based functional MRI studies show deficits in regions associated with inhibitory control and reward processing. Taken together, all of these different MRI studies implicate a consistent set of neural circuits related to attentional processes and inhibitory control, sustained attention, and motivation.

Genetic studies of ADHD have examined single candidate risk genes, genome-wide associations, rare chromosomal abnormalities known as copy number variants, and polygenic risk scores. Given the difficulty of linking genes to the diagnosis, attention has turned to endophenotypes—distinct heritable traits that lie on the path between genes and disorder. Endophenotypes may be more proximal to genetic influence than the disorder itself and more amenable to investigation. Candidate endophenotypes in ADHD include intra-individual reaction-time variability, response inhibition, and deficits in working memory. Whether specific abnormalities in neural circuits are related to cognitive endophenotypes remains to be seen.


**Cardiovascular Safety of Methylphenidate**

Use of methylphenidate (Ritalin) in children and adolescents is associated with increased risk of cardiac arrhythmia and myocardial infarction (MI), according to results of a population-based study. However, these events are uncommon and the absolute risk is likely to be low. There does not appear to be increased risk of other cardiovascular events.

**Methods:** Claims data were analyzed from South Korea’s national health insurance system for patients aged ≤17 years who had a diagnosis of ADHD. Methylphenidate prescriptions and the occurrence of cardiovascular events occurring in 2008–2011 were recorded. Each participant served as his or her own control, and the occurrence of cardiovascular events during each patient’s time exposed or unexposed to methylphenidate was compared. Methylphenidate exposure was divided into periods of 1–3 days, 4–7 days, 8–14 days, 15–28 days, 29–56 days, and >56 days. The analysis was adjusted for time-varying confounders, including age, comorbidities, and exposure to other psychoactive drugs.

**Results:** Of >144,000 children and adolescents with ADHD identified, about 114,600 received a new prescription for methylphenidate during the study period. A total of 1224 of these patients experienced a cardiovascular event: arrhythmias (n=864), hypertension (n=396), MI (n=52), stroke (n=67), and heart failure (n=44). The median age at first methylphenidate exposure was 11–13 years, as was the median age at first cardiovascular event.

The incidence of arrhythmia was increased during methylphenidate exposure of any duration (adjusted incidence rate ratio [IRR], 1.61). The highest risk was during the first 3 days of treatment; and risk returned to baseline levels after 56 days. Arrhythmia risk was higher during methylphenidate use in children with congenital heart disease (IRR, 3.49), but the incidence remained elevated in those without congenital heart disease.

Methylphenidate was not associated with hypertension overall, but risk was increased in the first week after the start of methylphenidate treatment (IRR, 1.29). MI risk was not elevated overall, but there was about a 2-fold increase in risk after the first week of treatment, lasting through the 56-day period and then diminishing. Methylphenidate was not associated with increased risk of stroke or heart failure.
Discussion: Previous studies have reported no association of methylphenidate with cardiovascular adverse events, but they may have lacked sufficient statistical power, given the rare occurrence of these events. The present study had an adequate sample size and was also able to produce risk estimates for different time periods. The results of this analysis are consistent with the biological mechanisms of these effects: immediate onset with arrhythmia and delayed onset with MI.

Shin J-Y, Roughead E, Park B-J, Pratt N: Cardiovascular safety of methylphenidate among children and young people with attention-deficit/hyperactivity disorder (ADHD): nationwide self controlled case series study. BMJ 2016; doi 10.1136/bmj.i2550. From Jewish General Hospital, Montreal, Canada; and other institutions. This study was conducted without external funding. The study authors all declared no competing interests.

*See Reference Guide.

Cardiac Safety of Antipsychotics

In a study in pediatric patients, QT interval and heart rate were not altered during the first year of treatment with the 3 most commonly prescribed second-generation antipsychotics.

Methods: Study participants (n=216) were children and adolescents who received treatment at 4 Spanish hospitals, either as outpatients or in short-term inpatient units. At their baseline visit, they were classified as either antipsychotic-naive (with no prior treatment) or quasi-naive (with their first prescription started within a month of study enrollment). The study included patients with any psychiatric disorder and those who received treatment concurrently with antidepressants, anticholinergics, mood stabilizers, or benzodiazepines. Electrocardiograms (ECGs) were performed at baseline and at 3-, 6-, and 12-month follow-up visits. For each patient, the corrected QT interval (QTc) was measured independently by 2 cardiologists. Because pathological levels of QTc are a matter of controversy, the authors chose a threshold, >440 milliseconds (ms), supported by recent pediatric cardiology literature.

Results: Of the 216 study patients, 137 received treatment with risperidone, 34 with olanzapine, 33 with quetiapine, and 2 with other drugs. Most patients (35%) had a diagnosis of schizophrrenia, schizoaffective disorder, or other psychotic disorder, followed by mood disorder (27%) and ADHD/behavior disorder (19%). The average age was 14 years, and the youngest patient was age 4 years. Four patients (<2%) had a personal history of cardiac disease, and 45 (22%) had a family history. Patients who received risperidone were younger than the others on average and less likely to be given a prescription for an SSRI.

The mean baseline QTc was 396.74 ms. The average QTc did not change during the study, no patient had a QTc >500 ms, and no patient had treatment stopped because of QTc elevation. There were no differences in mean QTc among the 3 drugs, between treatment-naive and quasi-naive patients, or according to age, diagnosis, cumulative medication exposure, alcohol use, or cannabis use. Baseline QTc values were higher in girls and in patients taking antidepressants and were lower in overweight patients, but all of these differences narrowed and became statistically nonsignificant with time.

At baseline, 9 patients had QTc intervals above the 440-ms cutoff. Elevations were observed in 9 patients at 3 months, 6 patients at 6 months, and none at 12 months. These elevations were not associated with individual drugs, the cumulative dose, or other factors. Average heart rate tended to decrease with time in the sample.

Discussion: These results support the cardiac safety of atypical antipsychotics, previously shown in a small number of pediatric safety studies. This study did not confirm previous inconsistent reports of heart-rate increases in young patients taking atypicals, nor did it confirm any risk factors for QTc prolongation suggested by previous research. The naturalistic
study design suggests the results can be generalized to different treatment settings. The authors recommend restricting follow-up ECGs in patients taking the 3 study drugs to those with clinical cardiac risk factors or congenital or family history of heart disease, and possibly those who gain weight during treatment.


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

Relative Antidepressant Efficacy

According to results of a network meta-analysis* of all available clinical trials, fluoxetine appears to be the best option among available antidepressants for children and adolescents.

Background: Antidepressants have previously been compared in pairwise meta-analyses, but this study appears to be the first network meta-analysis, a type of analysis that allows indirect comparisons between drugs based on their effects relative to placebo or other common comparators.

Methods: A comprehensive literature search identified 34 published and unpublished parallel randomized controlled trials conducted through May 2015 that investigated any antidepressant for acute treatment. Participants had mean ages ranging from 9 to 18 years and had a primary diagnosis of major depressive disorder, according to standardized criteria. The primary efficacy outcome was change from baseline to study endpoint in depressive symptoms, measured using the clinician-rated Children's Depression Rating Scale–Revised, the Beck Depression Inventory, or the Children's Depression Inventory. Secondary outcomes included response (≥50% symptom reduction), all-cause discontinuation, and suicidal behavior or ideation.

Results: The 34 randomized trials assessed 14 different antidepressants and had a mean sample size of 159 patients. The trials included 5260 participants, of whom 2154 received placebo. Most trials were 8 weeks in duration and enrolled patients with moderate-to-severe depression. Most studies (n=22) were industry-sponsored; 4 trials were rated as low risk of bias, 20 as moderate risk, and 10 as high risk.

The largest number of trials were comparisons of fluoxetine with placebo. In the network meta-analysis, fluoxetine was statistically superior to placebo (standard mean difference,* 0.51) and to several other drugs for the primary outcome. No other drug was superior to placebo. Results for the secondary outcomes of response and all-cause discontinuation were similar and supported the results of the main analysis. Fluoxetine was also rated as the best drug in terms of tolerability. Venlafaxine was associated with a higher risk of suicidal behavior or ideation compared with placebo (odds ratio,* 0.13 in favor of placebo), and compared with 5 other antidepressants. Many antidepressants lacked reliable data on risk of suicidality.

Discussion: The moderate effect size of fluoxetine raises doubts about whether this result is robust enough to inform clinical practice. Estimates of tolerability are also not easily interpreted because of large confidence intervals, potential biases, and small numbers of studies. Notwithstanding these concerns, fluoxetine
may be considered the best drug option in children and adolescents with major depression. However, its use should be limited to those with moderate-to-severe depression who have not had response with nonpharmacologic therapy or those who lack access to psychotherapy.

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


*Common Drug Trade Names:* amitriptyline—Elavil; citalopram—Celexa; clomipramine—Anafranil; desipramine—Norpramin; duloxetine—Cymbalta; escitalopram—Lexapro; fluoxetine—Prozac; imipramine—Tofranil; mirtazapine—Remeron; nefazodone—Serzone; nortriptyline—Pamelor; paroxetine—Paxil; sertraline—Zoloft; venlafaxine—Effexor

*See Reference Guide.

### Early Puberty and Adolescent Depression Risk

In a population-based study, early breast development was associated with increased risk of depression in adolescent girls. Early puberty did not increase depression risk in boys.

**Background:** A Hong Kong-Chinese national birth cohort was initially assembled in 1997 to investigate the effects of secondhand tobacco smoke on infants. The cohort consisted of nearly all children born in Hong Kong in April or May 1997. The same cohort was used to assess the effects of age at puberty onset on depression.

**Methods:** Puberty onset was assessed by physicians using the Marshall and Tanner stages during ongoing biannual school health examinations beginning in grade 2 (ages 6–7 years). Puberty onset was defined as Tanner stage II for development of breasts in girls and genitalia in boys and for pubic-hair development in both genders. Depressive symptoms were assessed between 2010 and 2012 using the 9-item Patient Health Questionnaire, with depression defined as a total score of ≥11 points. The statistical analysis was adjusted for socioeconomic position (known to influence both puberty onset and depression), body mass index, and other factors.

**Results:** More than 5500 children were included in the analysis. Depression was assessed at an average age of 13.6 years. The mean age of breast-development onset was 9 years; genital development occurred at a mean age of 11 years, and age at pubic-hair onset was nearly 11 years for girls and nearly 12 years for boys. In girls, early breast development was associated with a higher risk of depression (fully adjusted odds ratio,* 0.83). This odds ratio corresponds to a 17% reduction in risk of adolescent depression for every 1-year delay in breast development. Depression risk was not associated with development of the genitalia in boys or with the appearance of pubic hair in either gender.

**Discussion:** Previous studies from Western countries have found early puberty onset to be associated with depressive symptoms in girls, but the studies did not examine the role of specific indicators. The effect of early puberty on depression may be attributable to biological and/or social phenomena. Estradiol plays a key role in breast development and may increase girls’ sensitivity to negative psychological effects. Genital development in boys is driven by testosterone, and pubic-hair onset is a response to adrenal androgen production, hormones that may be emotionally neutral. Social context may play a role: Early puberty onset in girls can work against maintaining relationships and psychological well-being, but early puberty may increase status in boys. Whether the effects are sustained or transient remains to be seen.


*See Reference Guide.*
Reference Guide

**Incidence Rate Ratio:** The number of new cases of a condition in a defined (specified) group or population expressed as a ratio. For example, if there are 1000 people and a condition develops in 14 of them, the incidence rate is 14 per 1000 or 1.4%.

**Network Meta-Analysis:** A study design that can provide estimates of efficacy for multiple treatment regimens when direct comparisons are unavailable. This method extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common.

**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.

**Standardized Mean Difference:** The difference between 2 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.

**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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