

CHILD & ADOLESCENT PSYCHIATRY ALERTS

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Fluoxetine, Anger, and Neural Activation

In a group of adolescents with major depression, a single dose of fluoxetine (*Prozac*) altered the activity of components in the corticolimbic circuitry in response to angry facial expressions.¹ This observation may represent a key mechanism by which fluoxetine improves the response to anger and irritability and enhances self-regulation in adolescent depression.

Background: Irritability is a core symptom of major depressive disorder in adolescents but not adults. These authors previously found that fluoxetine reduced the recognition of anger in healthy subjects, aged 18–21 years,² consistent with the hypothesis that anger processing may be a core mechanism of fluoxetine action in this age group. The present experiment was designed to test whether this effect is associated with reduced neural activity in the amygdala and whether fluoxetine would increase activity in the dorsal anterior cingulate cortex (dACC), a region involved in self-regulation of negative emotions.

Methods: The study was conducted in adolescents, aged ≤ 17 years, with a primary diagnosis of major depressive disorder who were scheduled to begin treatment with fluoxetine. They were randomly assigned to receive a single, double-blind dose of 10-mg liquid fluoxetine or placebo, followed 6 hours later, when concentrations of fluoxetine were expected to be at their peak, by functional magnetic resonance imaging (fMRI). During the fMRI scan, participants were asked to rapidly identify the gender of faces expressing angry, happy, and fearful moods, a task that is sensitive to the acute effects of antidepressants on neural processing.

Results: The 29 participants had a mean age of about 16 years, had been experiencing depression for a mean of 14 months, and were in their first or second episode of major depression. In a whole-brain analysis, adolescents in the fluoxetine group showed reduced activation in a temporolimbic cluster in the left hemisphere, extending into the amygdala and hippocampus when exposed to angry faces, compared with happy faces ($p < 0.05$). The fluoxetine group also showed increased activation to happiness and reduced activation to anger compared with the placebo group. Region-of-interest analysis of the amygdala showed a near-significant ($p = 0.055$) interaction between emotion, hemisphere, and treatment group, with reduced activation in response to anger and increased activation in response to happiness in the fluoxetine group.

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A similar pattern was seen for the hippocampus, suggesting that both regions are involved in the effects of fluoxetine. The fluoxetine group had increased activation of the dACC in response to both happiness and anger ($p=0.044$).

Discussion: Previous studies in adults have shown that antidepressants have rapid effects on neural activity within hours of administration, before any clinical effects are noticed. These changes may be a critical mechanism by which antidepressants reduce negative biases and increase the processing of positive information, leading to clinical improvement. Future studies should evaluate whether these early effects are predictive of later symptomatic improvement.

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

¹Capitão L, Chapman R, Murphy S, Harvey C, et al: A single dose of fluoxetine reduces neural limbic responses to anger in depressed adolescents. *Translational Psychiatry* 2019; doi 10.1038/s41398-018-0332-2. From Oxford University Department of Psychiatry and Oxford Health NHS Foundation Trust, Oxford, U.K. **Funded by the John Fell Fund; and other sources. Three of 7 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

²Capitão L, et al: Acute fluoxetine modulates emotional processing in young adult volunteers. *Psychological Medicine* 2015;45:2295–2308.

*See Reference Guide.

Cognitive Performance in Schizophrenia

In a functional MRI study, cognitive control deficits were present at baseline in patients with new-onset schizophrenia. Over time, patients showed stable deficits and a pattern of performance that was similar to that of healthy controls. This finding argues for the neurodevelopmental hypothesis of the illness, which suggests deficits are present before symptoms appear, possibly reflecting CNS insults before birth or genetic predispositions. Deterioration after disease onset would have supported the neurodegenerative model, the alternative hypothesis.

Methods: Study participants were 87 patients, aged 12–25 years, with schizophrenia, recruited from a university-based early-psychosis program, and 93 healthy controls. All participants underwent fMRI at baseline. Additional evaluations were scheduled at 6, 12, and 24 months, but only 32 patients (37%) and 58 controls (62%) had usable data from ≥ 1 evaluation. Schizophrenia symptoms were rated using validated instruments, and scores were combined into the factors of reality distortion, disorganization, and poverty symptoms. Participants also completed a continuous performance task during fMRI to measure cognitive-control associated brain activity and behavioral performance. Whole-brain scans were obtained at baseline, and longitudinal activity analyses were conducted on left and right dorsolateral prefrontal cortex (DLPFC) regions of interest.

Results: Study participants had a mean age of 19 years and a mean symptom duration of 5 months before treatment. At baseline, three-fourths of patients were receiving an atypical antipsychotic or other medication. Across the age span, patients with schizophrenia performed more poorly on the baseline fMRI task than controls. Those receiving medication performed at an intermediate level between unmedicated patients with schizophrenia and healthy controls. Younger age at schizophrenia onset was not associated with poorer cognitive performance.

Baseline whole-brain scans showed reduced activation in the prefrontal cortex-parietal cognitive control network during test conditions in patients with schizophrenia, compared with controls of a similar age. However, the trajectory of DLPFC activation in longitudinal measurements in patients paralleled that of healthy controls. Cognitive performance and activation were not influenced by gender or the duration of untreated psychosis, but these outcomes were worse in patients with higher levels of reality distortion, disorganization, and poverty and with lower levels of function.

Discussion: These observations suggest that despite the presence of impaired cognitive performance at the onset of schizophrenia, brain maturation and development continue in young people, with a pattern that is comparable to that of their unaffected peers.

Niendam T, Ray K, Iosif A-M, Lesh T, et al: Association of age at onset and longitudinal course of prefrontal function in youth with schizophrenia. *JAMA Psychiatry* 2018;75 (December):1252–1260. doi 10.1001/jamapsychiatry.2018.2538. From the University of California, Davis, Imaging Research Center, Sacramento; and other institutions. **Funded by the Brain and Behavior Research Foundation; and the NIMH. The authors declared no competing interests.**

Genotyping for Risperidone Adverse-Event Risk

In a retrospective study, children and adolescents determined to be poor or intermediate metabolizers of the cytochrome P450 enzyme CYP2D6 were at increased risk of adverse events with risperidone (*Risperdal*). Pre-prescription genetic testing to identify high-risk status may be beneficial in patients already at increased risk for risperidone adverse effects or with conditions risperidone may aggravate, such as obesity or neurological disorders.

Background: Risperidone is primarily metabolized by CYP2D6, whose function varies from absent to ultrarapid. Studies in adults have linked CYP2D6 status with differences in risperidone pharmacokinetics, efficacy, and adverse effects. Previous data in children and adolescents are limited and inconsistent. There are no specific guidelines for prescribing risperidone based on CYP2D6 status.

Methods: Study data were collected from a biobank that linked DNA profiles to electronic medical records from a U.S. university medical center. Because a preliminary analysis found no risperidone adverse effects reported within the first 4 weeks of treatment, the study group consisted of patients who had a first prescription for risperidone before age 19 years, received treatment for ≥4 weeks, and had available DNA samples. The primary study outcome was any adverse event observed by patients, parents, or a physician, or documented by a laboratory test, and attributed to risperidone. The analysis grouped poor and intermediate metabolizers and compared them with normal and ultrarapid metabolizers.

Results: Of 520 risperidone-exposed children and adolescents, 257 met the study's inclusion criteria and had unambiguous CYP2D6 status. Patients had a median age of about 8 years when risperidone was initiated, three-fourths were boys, and 84% were white. The majority were normal CYP2D6 metabolizers. (See table.)

Risperidone adverse events according to CYP2D6 status			
CYP2D6 status	Number (%) of patients	% with adverse events	Combined % with adverse events
Poor	15 (6%)	33%	46%
Intermediate	18 (7%)	56%	
Normal	218 (85%)	27%	27%
Ultrarapid	6 (2%)	50%	

In total, 76 patients (30%) experienced an adverse event attributed to risperidone, the most common being weight change (9% of all patients), sedation (6%), and extrapyramidal symptoms (6%). Adverse events were twice as frequent in poor/intermediate CYP2D6 metabolizers as in normal/ultrarapid metabolizers (adjusted odds ratio,* 2.4; p=0.03). A small proportion (9%) of normal/ultrarapid metabolizers were taking ≥1 concomitant drugs known to strongly inhibit CYP2D6; these did not appear to affect risk of adverse events.

Discussion: Clinical CYP2D6 testing is available from both commercial and academic labs along with resources to assist in assigning metabolizer status. However, it would be difficult to provide overall genotype-guided prescribing advice for risperidone in children and adolescents because of the wide range of indications for the drug. In the present study, the high incidence of adverse events suggests children who take risperidone should be closely monitored and alternate treatments should be considered for those with impaired CYP2D6 function, and possibly for ultrarapid metabolizers as well.

Oshikoya K, Neely K, Carroll R, Aka I, et al: CYP2D6 genotype and adverse events to risperidone in children and adolescents. *Pediatric Research* 2019; doi 10.1038/s41390-019-0305-z. From Vanderbilt University School of Medicine, Nashville, TN. **Funded by Vanderbilt University; and other sources. One of 6 study authors disclosed a potentially relevant financial relationship; the remaining authors declared no competing interests.**

*See Reference Guide.

Weight Gain with Aripiprazole, Risperidone

In an observational study, children who received treatment with aripiprazole or risperidone gained excessive weight and then stabilized as overweight or obese during adolescence. Unexpectedly, aripiprazole was linked with more weight gain than risperidone, possibly as a result of its use following inadequate response with a first-line drug.

Methods: Study participants were outpatients enrolled in an ongoing pharmacovigilance program involving 4 second-generation antipsychotics. In this program, risperidone is used as first-line therapy, aripiprazole is second-line, and olanzapine and quetiapine are third-line. The sample consisted of patients, aged 6–17 years, receiving treatment for disruptive behavior disorders with either risperidone or aripiprazole monotherapy. Patients were followed for ≤ 2 years of treatment, and height and weight were measured every 3 months. The primary comparison was the body mass index (BMI) z score,* age- and gender-standardized to the general population of Italy, where the study was conducted. Weight changes were compared for the 2 drugs, for children (aged ≤ 13 years) versus adolescents, and for those who had or had not received previous antipsychotic treatment.

Results: A total of 127 patients received risperidone (n=103) or aripiprazole (n=24) and had ≥ 2 height and weight assessments after starting treatment (mean number of assessments, 3). At study entry, 76 patients (60%) were antipsychotic-naïve. The median BMI in the combined child–adolescent population was 20.9 at baseline and 21.6 at the last visit.

Of the predictive factors that were examined in a multivariate model, weight gain was significantly associated with the drug taken ($p < 0.01$) and age category ($p = 0.05$), but not with previous antipsychotic use. Both children and adolescents who took aripiprazole showed significant increases in BMI z scores, indicating greater weight gain relative to height than their peers. The increase was steeper in children than in adolescents. Children who took risperidone also had an average increase in BMI z score, but it was not statistically significant; the mean BMI z score did not change in adolescents.

Nearly half of the study patients had already been receiving pharmacotherapy (for 3–10 months on average) before beginning observation. The weight gain trajectories indicate changes in BMI z score are largest in patients with the shortest previous exposure to antipsychotics (i.e., children taking aripiprazole) and smallest in those with the longest previous exposure (i.e., adolescents taking risperidone). This observation, which is not surprising as antipsychotic-associated weight gain primarily occurs during the first 4–6 months of treatment, implies a plateau effect with longer drug exposure.

Discussion: Weight gain is an important limiting factor in the long-term use of second-generation antipsychotics. Whether liability for weight gain is age related is an important

question that can influence patient management. The present study suggests risperidone, and even more so aripiprazole, tilt the weight-change trajectory toward excessive gain until a plateau between excessive weight and obesity is reached during adolescence. The presence of overweight status at these levels can have serious future health consequences. The interpretation of these results should be tempered by a potential selection effect: Adolescent patients with a low propensity to gain weight were more likely to stay on their initial treatment and less likely to be switched to second-line treatment.

Pozzi M, Pisano S, Marano G, Carnovale C, et al: Weight-change trajectories of pediatric outpatients treated with risperidone or aripiprazole in a naturalistic setting. *Journal of Child and Adolescent Psychopharmacology* 2018; doi 10.1089/cap.2018.0092. From the Scientific Institute IRCCS Eugenio Medea, Lecco, Italy; and other institutions. **Funded by the Regional Centre of Pharmacovigilance of Lombardy; and other sources. The authors declared no competing interests.**

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

*See Reference Guide.

White Matter Alterations in Anxiety Disorders

A brain imaging study found reduced connectivity of the uncinate fasciculus (UF), a white matter tract critically involved in emotion regulation by linking the amygdala with regulatory prefrontal cortical regions, in preadolescent boys with anxiety disorders, but not in girls. This finding suggests early-life interventions directed toward restoring UF integrity could reduce anxiety symptoms by strengthening white matter connectivity.

Background: Previous studies, predominantly in adults with anxiety disorders, found reduced fractional anisotropy (FA), a measure of structural connectivity, of the UF. However, the phenomenon could theoretically result from illness chronicity or medication exposure.

Methods: The present study used diffusion tensor imaging to assess white matter integrity in 52 unmedicated preadolescent children with an anxiety disorder diagnosis and 46 age- and gender-matched controls. Diffusion measures were obtained for 7 different white matter tracts of interest, including the UF.

Results: The 98 study participants had a mean age of 10.5 years, and about half were girls. Children with anxiety disorders had significantly reduced UF FA compared with controls ($p < 0.001$; effect size, $* 0.73$). The UF was the only tract that differed between children with anxiety disorders and healthy comparison subjects. The significant difference was found only in boys; girls with anxiety disorders did not differ from their respective controls. In the sample as a whole, UF FA increased as a function of age but was not associated with comorbid ADHD or hormonal status. The other 6 white matter tracts were unaffected by anxiety disorders.

Discussion: The UF is the major tract connecting structures like the amygdala and hippocampus with the prefrontal cortex; alterations in its structure could affect information flow relevant to emotion regulation. The present results indicate diminished UF FA is present early in life in children with anxiety disorders and is not associated with disease chronicity or medication exposure. This suggests white matter alterations observed in adults with anxiety disorders may have their origin in childhood. It is possible that the developmental trajectory of UF FA differs between boys and girls, but this study found no age-by-gender interaction.

Tromp D, Williams L, Fox A, Oler J, et al: Altered uncinate fasciculus microstructure in childhood anxiety disorders in boys but not girls. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2018.18040425. From the University of Wisconsin, Madison; and other institutions. **Funded by the NIH. Three of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Clozapine REMS Update

The Risk Evaluation and Mitigation Strategy (REMS) Program for clozapine—designed to ensure patients have continued access to the drug as well as information on appropriate management of potential adverse effects, including severe neutropenia—is undergoing important changes. These modifications, summarized below, take effect on February 28, 2019.

- Both prescribers and pharmacies must be certified in the REMS program or they will no longer be permitted to prescribe/dispense clozapine. However, patients can no longer be enrolled in the REMS program by their pharmacist; all enrollments must be completed by the prescriber or their designee. If you prescribe clozapine in an outpatient setting but are not yet certified, you can complete the process at www.clozapinerems.com. Once a prescriber is certified, his/her prescriber designees must also enroll online.
- Clinicians who prescribe clozapine for an inpatient who is already enrolled in the program do not need to be certified in the REMS program. However, newly-treated patients must be registered in the REMS program prior to receiving their first dose.
- In accordance with the clozapine prescribing information, patients' absolute neutrophil count (ANC) must be monitored regularly. Values must then be submitted directly to the clozapine REMS database. While monitoring is required, outdated ANC levels will not prevent a pharmacy from dispensing clozapine. However, if the most recent ANC on file for a patient indicates moderate or severe neutropenia, the pharmacy will not be authorized to dispense the medication unless the prescriber documents that the benefits of clozapine treatment outweigh the risks associated with neutropenia by submitting a treatment rationale to the REMS program. These can be filed online at www.clozapinerems.com or by calling the Clozapine REMS Program Contact Center at 844-267-8678. If a patient does not have an ANC on file in the REMS database, the pharmacy will not be authorized to dispense clozapine.

The Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program Modification will go live on February 28, 2019. Available at www.fda.gov/Drugs/DrugSafety/ucm467560.htm.

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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.

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.

Z Score: A statistical measurement of a score's relationship to the mean in a group of scores. A z score of 0 means the score is the same as the mean.

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