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## Inside



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EDITORIAL

# Life, Death, and Mind-Body Medicine Across the Lifespan

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On June 6, 2015, an African American man from the Bronx hanged himself in his bedroom while his mother rested quietly downstairs. He concocted a rope from strips of bed sheets, a technique honed during five previous suicide attempts as an inmate at Rikers Island, the adult penitentiary in New York City where he was detained for 3 years. Two of those years were spent in solitary confinement, where he tried to take his life several times.

Wrongfully imprisoned at age 16, exonerated at 20, and dead at 22 by suicide, Kalief Browder's story is a tragedy of epic proportions.

His death reverberates with the unifying theme of this issue of the Residents' Journal: the inextricable bond between mind and body in children and adolescents. In each article, the false dichotomy of mind and body is undermined in its own way, effacing the ersatz distinction between the physical and mental. The mind, as psychiatrists know, can suffer mightily from insults to the body. And our bodies, of course, are vulnerable to the torment of mental illness.

But some minds and bodies are more vulnerable than others. Browder's case is so troublesome, in part, because a constellation of bodily and mental attributes and insults conspired to take his life too soon. Imprisoned as an adolescent at Rikers, he was one of the 6,000 minors detained in adult facilities that are inappropriate for youths and devastating to development (1). As an African American male, he was among the 1 in 3 black men that can expect to be incarcerated at some point in their lives, a rate six times higher than their white counterparts (2). As a body that was placed in "solitary confinement"—a euphemism for the barbaric practice of limiting social contact by isolating individuals in closed cells for 22 to 24 hours per day, for days to years on end—Browder endured the effects of a draconian method of cruel and unusual punishment. And of course, Browder suffered from mental illness. During and after his solitary confinement, he began to experience severe depression and debilitating paranoia; all of these factors ultimately culminated in his suicide. His race, age, isolation, and mental illness were all wielded against him to end his life too soon.

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"Mind-body medicine," the subtext of this issue on child medical conditions and psychopathology, has become a moniker for the frivolous pursuit of happiness by the worried well. Browder's story reminds us, however, that mind and body are not yoked exclusively in privileged circles. Oppressed bodies beget oppressed minds, and vice versa.

It is time we as psychiatrists take a closer look at the forces that colluded to end Browder's life, including the terrible ways in which the mistreatment of the body can produce disastrous and unconscionable effects on the mind.

Dr. Saunders is a second-year resident at the Child Study Center, Yale University, New Haven, Conn., and Guest Editor for this issue of the Residents' Journal.

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ARTICLE

# Lithium in Child and Adolescent Bipolar Disorder

Max S. Rosen, M.D.

Lithium was first used as a pharmacological agent in 1847 by Alfred Garrod, who prescribed the medication for "brain gout" (1). However, Dr. William Hammond at Bellevue Hospital, in 1871, was the first physician to prescribe lithium for mania "to diminish the amount of blood in the cerebral vessels, and to calm any nervous excitement that may be present" (1). John Cade reintroduced lithium to modern psychiatry in 1949, when he used it to treat 10 manic patients (1). By 1970, on the basis of four controlled trials of 116 adults demonstrating an average response rate of 78%, the Food and Drug Administration (FDA) approved lithium for acute mania in adults. It was not until the early 21st century that lithium became the first FDA-approved medication for the treatment of mania in youths aged 12–17, mostly based on adult trials (2). Given the dearth of methodologically stringent studies in the pediatric population, the FDA requested the creation of the Collaborative Lithium Trials to systematically assess lithium's efficacy and safety in pediatric bipolar disorder, a process that is still unfolding (3, 4).

## MECHANISM OF ACTION

The best evidence surrounding lithium's mechanism of action for antimanic properties involves the inositol depletion hypothesis (5). This hypothesis suggests that lithium dampens second messenger transmission by inhibiting inositol monophosphatase (IMPase). Since neurons cannot obtain free inositol from the plasma due to inositol's inability to cross the blood-brain barrier, neurons are solely reliant on IMPase to generate free inositol, important for neurons' second messenger systems. Therefore, when firing rates of neurons are abnormal, as in acute mania, lithium can dampen second messenger transmission. Finally, Chiu et al. (6) point to lithium's neurotrophic and angiogenic effects, which enhance synaptic plasticity.

## PHARMACOKINETICS AND DRUG INTERACTIONS

After oral administration, lithium is absorbed and reaches peak serum levels in 1–3 hours. Peak neural concentrations occur about 24 hours later due to the lower permeability of the blood-brain barrier (7). Lithium then circulates unbound to plasma proteins throughout total body water until the kidneys finally excrete it un-metabolized (5). Like sodium, lithium is 70%–80% reabsorbed by the proximal renal tubules, and because this reabsorption is competitive between lithium and sodium, anything causing sodium deficiency will increase serum lithium levels (5). For example, dehydration, sodium restriction, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, thiazide diuretics, and intrinsic renal disease will all acutely cause lithium levels to increase. The elimination half-life of lithium is 24+/–8 hours and is maximal in the first few hours after peak levels are achieved (7).

Findling et al. (3) found that when specifically tested in the pediatric population (average age: 11.8 years), the average half-life was 17.9 hours, and the investigators concluded that children have a shorter elimination half-life and greater clearance compared with adults due to the fact that clearance is correlated with total body weight and fat-free mass.

## CLINICAL USE

Optimal dosing strategies have been extensively studied in the pediatric literature. Findling et al. (8) argued for starting children, ages 7–17 and weighing 30 kg or more, on lithium 300 mg either twice or thrice daily and increasing the dose by 300 mg weekly thereafter, as tolerated to efficacy. This strategy yielded mean total daily doses of 1500.0 mg (SD=400.9 mg) and a mean weight-adjusted total daily dose of 29.1 mg/kg/day. The mean serum concentration was accordingly 1.05 mEq/L.

As in adults, target serum concentrations in pediatric acute mania range from 0.8 to 1.2 mEq/L, with toxic effects and cessation of dose escalations occurring between 1.2 and 1.4 mEq/L (3, 4). Since the clearance of lithium is decreased overnight, bedtime doses can be reduced, with subsequent improvement in tolerability as a result of the decreased dose (7). This dosing structure thus allows for less polyuria, reduces problematic sedation and fatigue, and over time may reduce renal glomerular abnormalities.

## CLINICAL EFFICACY

Although lithium has consistently proven to be efficacious and acceptable in the treatment of adult acute mania (9), the results have been less conclusive in the treatment of acute pediatric mania. Following a review of four pediatric open-label trials of lithium in mania from 1989 to 2010, which indicated a collective average response rate of 40%, more recent systematic work has assessed lithium's clinical efficacy (10).

Masi et al. (11) performed a naturalistic study in which 282 children (mean age: 13.8 years) meeting DSM-IV criteria for mania or hypomania initially received monotherapy with lithium or valproate. For those who did not respond, as defined by a Clinical Global Impression-Improvement scale (CGI-I) score of 3 or

higher, the other mood stabilizer (or an antipsychotic for psychotic symptoms) was added according to clinician judgment. Sixty percent of patients treated with lithium (either monotherapy or combination) responded at 6 months. Although patients often received polypharmacy with antipsychotics, selective serotonin reuptake inhibitors, and stimulants, this study provides a real-world example indicating that polypharmacy may provide additional benefits in naturalistic settings, with lithium as a beneficial option.

The Treatment of Early Age Mania (TEAM) study (12, 13) assessed possible treatment paradigms in pediatric mania. Phase one (12) studied 279 children, ages 6-15, with DSM-IV bipolar I disorder (manic or mixed state) in a controlled, randomized 8-week study protocol. Response was defined as scoring 1 or 2 on the CGI-BP-IM scale. Phase one demonstrated risperidone's superiority to both lithium and valproate, with response rates of 68.5%, 35.6%, and 24.0%, respectively. It should be noted that at baseline, 77.1% of the patients had psychotic features. For the 64 subjects without psychosis, the greater response rate of risperidone versus lithium was not statistically significant.

Phase two studied the 89 nonresponders and 65 partial responders from phase one for an additional 8 weeks. The nonresponders were randomly switched to one of the other medications, while the partial responders received one of the other medications as an add-on. Though nonresponders who were switched to risperidone responded more frequently than those who were switched to lithium (47.6% versus 12.8%; p=0.005), the higher response rate of the partial responders receiving add-on risperidone (53%) versus add-on lithium (26.7%) was nonsignificant. Therefore, the results of the TEAM study indicate that in a pediatric population with heavy psychosis at baseline, although risperidone outperformed lithium for first-line treatment, lithium might be reasonable to add-on in children partially responding to risperidone or valproate.

Finally, Findling et al. (14) performed a randomized, double-blind placebo-controlled study of lithium in the acute treatment of mania. Eighty-one children, ages 7–17, diagnosed with DSM-IV bipolar disorder (manic or mixed episode) qualified for this 8-week study. The primary outcomes analyzed the change in Young Mania Rating Scale (YMRS) scores, while secondary measures assessed response and remission, defined as greater than 50% reduction in baseline YMRS scores, CGI-I scores of 1 or 2, YMRS scores less than 13, and CGI-severity scores less than 3, respectively. Lithium was significantly greater at reducing manic symptoms as measured on the YMRS (p=0.03). Superiority of lithium over placebo in response (32% versus 21%) and remission (26% versus 14%) fell short of statistical significance.

Several other pediatric trials discuss lithium's efficacy in maintaining stability after acute mania response (15), treating depressive symptoms of pediatric bipolar disorder (16), and improving behavior in children with conduct disorder (17).

For acute mania, however, more placebo-controlled studies, which take into account the complexity of diagnosing pediatric mania (18), are required to support the clinical consensus that lithium is a first-line treatment for pediatric bipolar disorder. However, as more children seemingly present with comorbidity, lithium's clinical efficacy–and treatment of pediatric bipolar disorder in general–may be improved with more than one mood stabilizer (11, 15).

**TABLE 1. Effects of Lithium (by Organ System)**

| Organ System | Effect |
|---|---|
| General | Edema, weight gain |
| Gastrointestinal | Nausea, vomiting, diarrhea, abdominal pain |
| Renal | Polyuria, elevation of creatinine |
| Neurologic | Action tremor (7-16 Hz), lethargy, weakness, cognitive "graying" |
| Endocrinologic | Hypothyroidism, hyperparathyroidism |
| Cardiac | Arrhythmias (sinoatrial node dysfunction) |
| Dermatologic | Acne, psoriasis activation |
| Hematologic | Benign leukocytosis |

## SIDE EFFECTS

The most cited adverse effects, most of which were studied in adult populations, are presented in Table 1 (5). The aforementioned clinical pediatric trials have reported the most common adverse effects associated with lithium to be gastrointestinal discomfort, weight gain, headache, and tremor (4, 10, 12, 14, 15). While less common, other potential side effects include leukocytosis, hypothyroidism, and renal tubular dysfunction. Additionally, though an association between lithium exposure and Ebstein's anomaly has been reported, no causal relationship has been established, and the absolute risk remains less than 0.1% (19). As a result of these adverse effects, treatment guidelines (18) indicate that baseline workup prior to initiating lithium includes a complete blood count, thyroid and renal function tests, and pregnancy test. Once achieving a stable lithium dose, lithium levels and renal and thyroid function tests, every 3–6 months, are warranted. In adult studies, most of the adverse effects are dose-dependent and thus improve with reduction in dosage. Other off-label treatment options for problematic adverse effects include amiloride for polyuria, beta-blockers for tremor, and levothyroxine for hypothyroidism (20).

## CONCLUSIONS

Lithium is a useful and safe medication in the treatment of acute mania in children and adolescents with bipolar disorder. It is a medication that has been studied in modern psychiatry since 1949 and functions likely by depleting inositol in neurons. While it does not affect other drug levels, its own drug level, which correlates with efficacy, is affected by several medications and physical conditions. It is generally tolerated, but several treat-

## KEY POINTS/CLINICAL PEARLS

- In recent systematic studies, lithium salts are demonstrating efficacy for improving acute manic symptoms, as well as weaker evidence for maintenance and anti-depressive treatment in pediatric bipolar disorder and anti-aggressive properties in pediatric conduct disorder.
- Lithium achieves its antimanic activity likely through depleting inositol from neurons.
- Lithium displays linear pharmacokinetics and is excreted renally, with levels most commonly affected by dehydration, some diuretics, nonsteroidal anti-inflammatory drugs, and angiotensin converting enzyme inhibitors.
- Like in the adult population, lithium is dosed to target serum levels of 0.8–1.2 mEq/L for acute mania in b.i.d.-t.i.d. dosing, with the most common side effects including gastrointestinal distress, polyuria, hypothyroidism, tremor, and weight gain.

ment-emergent effects exist, such as gastrointestinal, thyroid, renal, and weight abnormalities. Though pediatric bipolar disorder includes symptoms such as irritability and other symptoms shared by other pediatric psychiatric conditions (18), lithium has increasingly proven efficacious in the treatment paradigm of pediatric bipolar disorder.

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ARTICLE

# Pediatric Delirium

Robyn P. Thom, M.D.

Delirium, an acute transient disorder of global brain function, is becoming increasingly viewed as a psychiatric emergency in adult medicine. In adults, both the public health and individual patient burdens of delirium have proven to be extremely high. Delirium is present in 49% of all adult inpatient hospital days, resulting in an additional $16,303–$64,421 per delirious patient per year (1). Furthermore, the one-year risk of mortality associated with delirium in adults is 35%–40% (2). According to DSM-5, delirium is a disturbance in attention or awareness accompanied by changes in cognition that develops over a short period of time, fluctuates in course, and is the result of a medical condition (3). This definition of delirium can be difficult to apply in the pediatric setting, however, as a child's premorbid neurocognitive stage and language abilities must be taken into account. While neither DSM-5 nor ICD-10 includes a definition of delirium specific to pediatrics, multiple validated tools for assessing pediatric delirium have recently been developed. With these additional diagnostic tools, delirium is becoming increasingly recognized in children. Pediatric delirium comprises 10% of all pediatric consultation-liaison consults, occurs in up to 29% of critically ill children, and is a marker of serious illness, with an associated mortality rate of 20%. (4, 5). As noted by Schieveld and Janssen (6), timely recognition and treatment of pediatric delirium is necessary because the hypermetabolic state associated with delirium may impair recovery from critical illness, agitated behaviors associated with hyperactive delirium impede care, and the psychological effects may be traumatic.

## CLINICAL CHARACTERISTICS OF PEDIATRIC DELIRIUM

As in the adult population, delirium in the pediatric population can be classified based on the psychomotor state into hyperactive, hypoactive, or mixed delirium (7). While many of the clinical features of adult delirium can be applied to children, certain features are more prominent in children, which necessitate a unique approach to the pediatric delirium examination. For example, in a preverbal child the examiner might forgo formal bedside tests of attention and instead assess inattentiveness by observing poor eye contact or difficulty with engagement. Caregiver involvement can prove very helpful in making this diagnosis. Features of delirium that are particularly prominent in the pediatric population include irritability, affective lability, agitation, sleep-wake disturbance, and fluctuations of symptoms. In contrast, delusions, hallucinations, speech disturbances, and memory deficits are less commonly seen in children. Unique features of pediatric delirium include developmental regression with loss of previously acquired skills, inability of the usual caregiver to console the child, and reduced eye contact with the usual caregiver (8). Schieveld and Janssen (6) also described the "inconsolable child" as a red flag for delirium. A child who is agitated, breathing against the ventilator, and receiving escalating doses of sedating medications, should be considered to be delirious until proven otherwise (6).

## SEQUELAE OF DELIRIUM

Research on the sequelae of pediatric delirium remains in its infancy. Unlike in adults, research has not yet shown that an episode of pediatric delirium increases mortality independently of illness severity. However, Turkel et al. (4) demonstrated an increased length of hospital stay associated with a diagnosis of pediatric delirium. Furthermore, one-third of patients discharged from a pediatric intensive care unit meet criteria for posttraumatic stress disorder (PTSD) 3 months after discharge. Since PTSD symptoms can occur even in children who lack conscious memory of the trauma, delirium is a likely contributor to this finding (9). In the adult literature, it is becoming increasingly recognized that delirium can have negative long-term neurocognitive effects; however, it remains unclear whether this holds true for children. Early studies comparing generally medically hospitalized children to critically ill children show that critically ill children have impaired visual and spatial memory, as well as impaired attention, suggesting that an episode of pediatric delirium may affect long-term brain function (10).

## DIAGNOSIS

Pediatric delirium remains vastly underdiagnosed both by pediatric and psychiatric teams (11). There are a number of challenges associated with accurately and systematically diagnosing pediatric delirium. Because of inherent communication limitations in evaluating preverbal or nonverbal children, the diagnosis is contingent on close observation of behavioral symptoms. Additionally, the symptoms of pediatric delirium can be subtle, can vary depending on developmental stage, and are complicated by developmental variability. Involvement of the caregiver, who may not be easily accessible, is necessary to make a diag-

nosis. Finally, many of the symptoms used to make a diagnosis of pediatric delirium overlap with a number of other conditions, such as pain, distress, or drug withdrawal.

Fortunately, several delirium rating scales have recently been developed and validated. The Pediatric Anesthesia Emergence Delirium Scale, the Pediatric Confusion Assessment Method for the ICU, the Cornell Assessment of Pediatric Delirium, and the Sophia Observation Withdrawal Symptoms-Pediatric Delirium Scale comprise the four validated delirium screening tools for children. With comparable sensitivity (83%–94%), specificity (79%–98%), and feasibility of use, there is no clear "best" tool (12). However, the advantage in using a validated tool is increased rates of routine screening, thereby improving diagnostic accuracy and implementation of treatment.

The role of adjunctive tests to make the diagnosis of delirium remains limited. EEG shows diffuse slowing in only 65%–86% of pediatric cases, with fluctuations that parallel the clinical state (8). A number of candidate biomarkers, including hemoglobin-beta, S100 calcium-binding protein B, and IL-6 for delirium are being investigated; however, they are not routinely used to make the diagnosis. Thus, pediatric delirium fundamentally remains a clinical diagnosis.

## MANAGEMENT

Inouye's (13) three-pronged approach for the management of adult delirium can readily be adapted for the pediatric patient. Her approach includes identifying and addressing predisposing factors and providing symptomatic care and symptom-targeted treatment. Firstly, all delirious patients should undergo a thorough assessment to identify the underlying cause of delirium, with special attention to the three most common causes of delirium in children: infection, medication-related factors, and autoimmune-related factors (4). The most common deliriogenic medications include anticholinergic agents, benzodiazepines, and opioids. These medications should be minimized, substituted, or tapered as medically appropriate. In the adult literature, there is increasing evidence for use of dexmedetomidine as an alternative, non-deliriogenic sedative agent; however, this has not been studied in children. Secondly, supportive care in delirium includes addressing volume and nutritional status, early mobilization, and deep venous thrombosis prophylaxis. Finally, delirium symptoms should be managed as they arise. Behavioral strategies can include frequent presence of the caregiver, having a familiar toy or photographs available, avoiding physical restraints, and normalizing the sleep-wake cycle.

Generally, pharmacologic intervention is recommended when the patient is distressed by the symptoms, the symptoms impose a safety concern, or they are impeding advancement of medical care (14). While there are no agents with Food and Drug Administration approval for delirium treatment in either adults or children, antipsychotics have been clinically shown to address delirium symptoms in adults and are widely used. Since there are few studies that examine the safety and efficacy of antipsychotics in pediatric delirium, the current psychopharmacologic approach to managing pediatric delirium is modeled on experience in adults.

Generally, while atypical antipsychotics are favored over typical antipsychotics in children, both are used, and no formal guidelines exist to guide antipsychotic selection. A retrospective study of 110 children aged 1–18 years diagnosed with delirium showed that delirium scores decreased significantly with atypical antipsychotic use (15). In the study, olanzapine and risperidone were used based on provider preference. Rates of delirium resolution were similar between the two antipsychotics. Few adverse side effects were observed: only one patient developed mild dystonia, which resolved quickly with dose reduction, and no cardiac or metabolic side effects were observed. Both quetiapine and intravenous haloperidol have also been shown to be generally safe and efficacious in managing pediatric delirium (16, 17). However, in a separate retrospective study of 26 acutely ill children who received haloperidol for hyperactive delirium, 23% experienced adverse reactions, including dystonia and hyperpyrexia (18). Another observational study of two cases of delirium in adolescent girls suggests that the particular subtype of delirium may predict a differential response to antipsychotics, with hyperactive delirium being more responsive to haloperidol and mixed/hypoactive delirium being more responsive to risperidone (7).

### KEY POINTS/CLINICAL PEARLS

- Pediatric delirium occurs in 29% of critically ill children.
- Hallmarks of pediatric delirium include irritability, affective lability, agitation, sleep-wake disturbance, and fluctuations of symptoms.
- Consider pediatric delirium in the "inconsolable" or "non-sedatable" child.
- Antipsychotics are generally safe for managing delirium in children.

## PREVENTIVE STRATEGIES

In adults, delirium incidence can be robustly and safely reduced both by multicomponent non-pharmacologic approaches and antipsychotic use (19, 20). In contrast, little has been published on delirium prevention strategies in children. It may be prudent to consider adapting adult preventative strategies for high-risk children.

## CONCLUSIONS

Delirium, a syndrome of acute brain failure caused by medical illness, is becoming increasingly recognized in children. Although research in this field remains limited, early studies indicate that it is common, likely has negative long-term sequelae, and is treatable with both nonpharmacologic and pharmacologic approaches.

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CASE REPORT

# Very Early-Onset Schizophrenia in a Six-Year-Old Boy

Samantha Slomiak, B.S., Dena R. Matalon, M.D., Lisa Roth, M.D., M.S.

Very early-onset schizophrenia is characterized by hallucinations, delusions, and cognitive impairment in children less than 13 years old. The prevalence of very early-onset schizophrenia is unknown but is estimated to be 1:30,000 children. Very early-onset schizophrenia is the pediatric counterpart to early-onset schizophrenia, which affects adolescents 13–18 years old, and adult-onset schizophrenia, which affects individuals over 18 years old (1). Although the DSM does not differentiate between very early-onset schizophrenia, early-onset schizophrenia, and adult-onset schizophrenia, the age at onset of schizophrenia can have distinct clinical ramifications. Very early-onset schizophrenia tends to present insidiously, with a premorbid period characterized by developmental delay and diminished school performance. Oftentimes, children with very early-onset schizophrenia are misdiagnosed with pervasive developmental disorder before they develop florid psychosis (2). As very early-onset schizophrenia progresses, it shares more clinical features with early-onset schizophrenia and adult-onset schizophrenia, including hallucinations, delusions, and paranoia. However, it tends to be more severe and disabling than adult-onset schizophrenia, resulting in lower educational performance and poorer social relationships (1). It is also characterized by a higher rate of cytogenetic abnormalities than adult-onset schizophrenia (3), suggesting that affected individuals carry an even stronger genetic predisposition to schizophrenia. We describe the case of a 6-year-old boy with new-onset schizophrenia, who showed unusual behavior suggestive of psychotic symptoms as early as infancy.

## CASE

"Kyle" is a 6-year-old boy with a history of mild developmental delay who presented with one month of disorganized behavior, hallucinations, and developmental regression. At 3 months old, he began tracking objects his parents were unable to see. At 7 months old, he began visually fixating on unseen objects and would "open his eyes widely, become very excited, flap his arms, and tense his legs," according to his mother. He did not begin walking until 20 months old and was referred to early intervention for gross motor delay. At age 3, he began talking to someone his parents could not see, leading them to believe he had an imaginary friend. While learning to read at age 5, he would say, "Stop mom! The words are talking back!" This possibly suggests an experience of auditory hallucinations. In kindergarten, he was held back due to poor attention but remained socially interactive without grossly abnormal behavior. Then, one month prior to admission, he developed frank hallucinations and severe social withdrawal. He frequently whispered to himself nonsensically and was so internally preoccupied that he often was unable to follow commands. The patient's family history was notable for 1) schizophrenia in a maternal cousin, two paternal cousins, and his paternal great grandmother; 2) bipolar disorder in two paternal cousins; and 3) autism in a paternal cousin and a paternal great aunt. His pediatrician performed a preliminary workup, including routine laboratory examination and a CT of the head, which were normal. The pediatrician referred the patient for admission to our hospital.

On initial evaluation, the child appeared thin and younger than his stated age. His mother stated that he had been eating only intermittently, resulting in significant weight loss and failure to thrive (body mass index=14.5, weight <10th percentile; height <3rd percentile). His behavior was notable for stereotyped pursing of his lips, repetitive blinking, and poor eye contact. The child was mumbling to himself, and upon questioning, his speech was impoverished and disorganized. His affect was flat and intermittently guarded. He endorsed visual hallucinations of "people in [his] eyes" who were "following [him] everywhere," named "Shavonni, James, and Jack," who appeared "black with yellow teeth and green eyes." The child's mother endorsed that he had a history of paranoid delusions that people were chasing him or taking away his food. He expressed passive suicidal ideation, saying, "God said it's time for me to come to heaven," as well as homicidal ideation toward an unclear target, saying "I'm gonna cut you up; I'm gonna kill you." He did not exhibit self-injurious or violent behavior.

The patient received a comprehensive medical workup, including MRI of the brain, lumbar puncture (with oligoclonal bands, myelin basic protein, paraneoplastic, and N-methyl-D-aspartate receptor antibody testing), EEG, rheumatologic screening (with antinuclear antibody, C-reactive protein, erythrocyte sedimentation rate, ceruloplasmin, celiac, and thyroid testing), metabolic screening (with lactate, pyruvate, acylcarnitine, urine organic acid, and plasma amino acid testing), urine drug screen, and heavy metal panel, which were normal. The consulting psychia-

trist deferred initiation of antipsychotic medications given the patient's age and instead started clonazepam for agitation control. Given the patient's unusually young age at presentation, possible lifelong symptoms, and a strong family history of mental illness, he was referred for genetic testing. Chromosome single nucleotide polymorphism microarray analysis showed a 22q11.2 deletion (low copy repeat-A/low copy repeat-D).

**KEY POINTS/CLINICAL PEARLS**

- Very early-onset schizophrenia is defined as the onset of schizophrenia in children less than 13 years of age; DSM criteria for diagnosis are the same as adult-onset schizophrenia.
- Very early-onset schizophrenia has a premorbid period characterized by global delay in domains of motor, speech, social, and cognitive development; it is often misdiagnosed as pervasive developmental disorder due to the presence of stereotypy.
- The genetics of schizophrenia are largely unknown; the 22q11.2 microdeletion is the only copy number variation associated with schizophrenia.

## DISCUSSION

22q11.2 deletion syndrome is the most common chromosomal microdeletion syndrome. The 22q11.2 region contains large areas of low copy repeats, which are subject to meiotic error, resulting in recombination and subsequently deletions, most commonly between low copy repeat-A and low copy repeat-D. The syndrome encompasses a wide spectrum of manifestations, including congenital heart defects; chronic infections; palatal, parathyroid, and gastrointestinal abnormalities; and behavioral differences. Oftentimes, children with 22q11.2 deletion syndrome have speech delay, with their first words at 24 months (4). Perhaps most concerning, 75% of individuals with 22q11.2 deletion syndrome are affected by psychiatric illness, most commonly autism, attention deficit hyperactivity disorder, anxiety, and psychosis. Specifically, patients with 22q11.2 deletion syndrome are at a 25-fold increased risk for developing a psychotic disorder compared with the general population, and nearly 25% of these patients develop schizophrenia (5).

Twin, family, and adoption studies have shown that hereditary factors have a strong influence on the development of schizophrenia (6). However, only several genomic regions have been linked to schizophrenia, and there have been no individual causative genes identified. The 22q11.2 microdeletions are the only confirmed copy number variation known to cause schizophrenia (7). The genetics of schizophrenia appear to be highly complex, with numerous genes of minor effect interacting with each other to produce the phenotype. Attention has most recently turned to the role of epigenetics in the development of disease (6). It has been hypothesized that the genes responsible for the development of schizophrenia might be abnormal transcriptional units that code for RNA regulators of protein coding gene expression, rather than abnormalities in the coding genome itself (8).

The above case not only underscores the heritability of schizophrenia, but also is noteworthy for the clinical signs that preceded the patient's first break psychotic episode. Delayed milestones in all domains, including motor, speech, social, and cognitive development, characterize the premorbid period of schizophrenia. This effect is more pronounced in those with very early-onset schizophrenia than in those with early-onset or adult-onset schizophrenia (9). Stereotyped behaviors, such as flapping and echolalia, are also frequently present and can lead to a misdiagnosis of pervasive developmental disorder (2). Additionally, the premorbid period of very early-onset schizophrenia is often punctuated by declining academic function, with accelerating deterioration when the acute psychotic phase approaches. In the above case, the patient presented with nearly all of these predictive clinical signs, including developmental delay, stereotypy, and a decline in academic performance necessitating withdrawal from kindergarten.

Many clinicians are hesitant to make a diagnosis of very-early onset schizophrenia, with an average of 2 years from onset of symptoms to diagnosis. One challenge to diagnosis lies in the decision to attribute hallucinations to a pathological process given that non-pathological hallucinations occur in 8% of children. Contextual information is essential in making these distinctions, with special attention to the preservation of social relationships, higher premorbid functioning, and environment-specific symptoms (2, 9). Once a diagnosis is made, considerable controversy exists surrounding the use of antipsychotics in children due to limited data on safety and efficacy. Antipsychotics are generally recommended for severe cases, with evidence to suggest that early initiation improves outcomes, especially control of positive symptoms. The present case highlights that subtle clinical signs, including developmental delay, stereotypy, academic decline, and possible hallucinations, can herald the development of very early-onset schizophrenia.

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CASE REPORT

# Amelioration of Aggression and Echolalia With Propranolol in Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a neurodevelopmental disease that affects 1.5% of children. ASD presents with impaired social communication and restrictive behaviors and interests (1). Social communication deficits include difficulties with eye contact, body language, and verbal language, while restrictive behaviors include motor stereotypies and fixed behavioral routines (2). A characteristic of ASD is onset of poor social communication and stereotypies before 2 years of age, though the mean age of diagnosis is 5 years. While the etiology is unknown, most studies suggest that a combination of genetic and environmental factors are responsible, with neuroanatomical abnormalities in the limbic system, cerebellum, and cortex (3).

While there is no cure, existing treatments can alleviate disease symptoms and increase the patient's social and occupational functioning. High-functioning patients can lead independent lives, while low-functioning patients may require lifelong care in a dedicated facility (4). The only Food and Drug Administration (FDA)-approved pharmacotherapies for irritability in ASD are the atypical antipsychotics risperidone and aripiprazole (5, 6), but other antipsychotics (alpha-2 agonists, stimulants, antidepressants, and N-acetylcysteine [7, 8]), can treat the behavioral alterations (see Table 1). We present a case of an adult male with ASD who was hospitalized for aggression and violence and improved with propranolol monotherapy. We discuss the role of the autonomic system in ASD and evidence for treatment with non-selective beta-blockers.

## METHODOLOGY

The case is discussed in the context of the literature on the use of beta blockers in ASD. A literature review was performed through searches on PubMed using the keywords "autism," "autism spectrum," "beta-blocker," "propranolol," "autonomic," and "sympathetic." Inclusion criteria were use of a beta blocker for adult patients with ASD-related aggression. Articles addressing adrenergic function in ASD were also included.

## CASE

"Mr. C" is a 25-year old Caucasian man with ASD who was admitted to the hospital due to "getting angry at home" for over a month. Six weeks prior to presentation, the patient had expressed a desire to attend a prestigious university; his mother informed him that this was impossible because he had not completed his high school diploma. Discussions between the patient and his mother became increasingly heated, and the patient began to exhibit behavior that ranged from verbal insults to destruction of doors and windows in their shared home. Mr. C's previously fluent speech began to include stuttering and echolalia, which were mild prior to his exacerbation. His past medications included clomipramine, risperidone, and pemoline (a dopaminergic stimulant), but he had been stable off of medication prior to this exacerbation.

When initially evaluated, the patient refused to speak to the treatment team, paced the hallways, hit furniture, and shouted at staff and other patients. His heart rate was 102 beats per minute but normotensive. He displayed impulsive and inappropriate behaviors that included shouting jokes into the telephone handset, pacing the hallways, knocking on other patients' doors, and initiating loud conversations with inappropriate laughter. When playing board games, he would exhibit aggressive outbursts and sweep the game pieces off the board when he lost. Throughout his hospital stay, he stuttered during single sentences and experienced episodes of noticeable echolalia. A basic metabolic panel, lipid panel, and electrocardiogram obtained on admission were normal.

Monotherapy with the beta blocker propranolol 20 mg twice daily was started for behavioral and verbal control and its known benefit in the treatment of neuroleptic-induced akathisia, which was a possible contributor to Mr. C's agitation from prior antipsychotic use. Two days later, he impulsivity subsided, and he participated in group activities on the unit without disruption. Four days into treatment, he developed friendships on the unit, held quiet conversations, and engaged in board games without anger. He tolerated emotional conversations, such as discussion of delaying college plans, and the frequency of stuttering and echolalia decreased. He denied any side effects. His blood pressure remained at his baseline of 110/80 mmHg, and his heart rate decreased to 80 beats per minute. With the behavioral improvement on propranolol and stable vital signs, the patient was safely discharged without additional medications.

## DISCUSSION

### The Adrenergic System in ASD

Along with social dysfunction and restricted behaviors, ASD is often accompanied by impulsivity, anxiety, and aggression that resemble states of autonomic arousal (9). Autistic children demonstrate monoamine-induced tachycardia and elevated electrodermal conductance (a measure of sweat production from autonomic activation) (10) at when baseline compared with children

**TABLE 1. Representative Medications for the Control of Aggressive Behaviors in Autism Spectrum Disorder[a]**

| Medication | Class | Evidence[b] | Outcome | Study |
|---|---|---|---|---|
| Risperidone | Atypical antipsychotic | RCT | Significant reduction of irritability with risperidone versus placebo | McCracken et al. (5) |
| Aripiprazole | Atypical antipsychotic | RCT | Significant reduction of irritability with aripiprazole versus placebo | Marcus et al. (6) |
| N-acetylcysteine | Glutamatergic modulation | RCT | Significant reduction of irritability when N-acetylcysteine added to risperidone | Nikoo et al. (8) |
| Clonidine | Alpha-2 agonist | RCT | Modest improvement of hyperactivity and irritability with clonidine versus placebo | Jaselkis et al. (13) |
| Propranolol | Beta-adrenergic blocker | Case series | Remission of destructive behavior in half the patients treated with propranolol or nadolol | Ratey et al. (17, 18) |
| Nadolol | Beta-adrenergic blocker | Case series | Remission of destructive behavior in half the patients treated with propranolol or nadolol | Ratey et al. (17, 18) |

[a] All medications showed demonstrated benefit in the respective studies; RCT=randomized controlled trial.
[b] Evidence refers to the highest-quality study format available.

without ASD, similar to the tachycardia exhibited by our patient on admission (11), markers that are associated with aggression (9). While normal subjects demonstrate increased sympathetic arousal during active tasks, individuals with ASD may display paradoxically increased parasympathetic activity, as measured by heart rate variability, compared with controls (12). These findings may suggest that the repetitive behaviors of the disorder (echolalia in the above case) may be an adaptive response to this heightened autonomic activity.

### Therapeutic Use of Beta Blockers in ASD

The findings of sympathetic activation in ASD suggest that sympatholytic drugs may improve the behavioral symptoms of the disorder, as demonstrated by the efficacy of alpha 2 agonists for aggression in placebo-controlled trials (13). Though there are myriad reports of beta blockers improving aggression in patients with brain damage, mental retardation, and adult-onset psychiatric conditions (14–16), only two studies from a single cohort of eight adult patients have addressed the use of beta blockers for ASD-associated impulsivity and aggression. Both were open trials without controls, and both demonstrated remission of tantrums, property destruction, and self-injurious behavior in one-half the patient samples after 6 weeks of treatment with the non-selective beta blockers propranolol or nadolol (17). These trials revealed subtler improvements in speech and social behavior in all eight subjects (18), consistent with controlled trials demonstrating improvement of word fluency (19) and conversational reciprocity (20) with propranolol in ASD. In comparison, the response of the above patient in the present case report during the first week of treatment was faster than that of the patients in these studies and at a lower dose of propranolol (40 mg per day versus at least 100 mg per day). Additionally, nadolol does not penetrate the blood-brain barrier (21), suggesting that peripheral beta blockade may be sufficient to ameliorate aggressive symptoms. No studies, to our knowledge, have examined the effects of ß1-selective blocking agents on the symptoms of ASD, and this remains an avenue for further research.

### Limitations

The trials discussed above and in our case involved the use of beta blockers in adult autistic patients. It is unclear whether children might benefit, and the risk of hypotension may be dangerous in this age group. The beta blockers used were non-selective ß1 and ß2 antagonists, and the results from the trials and our case report cannot be applied to ß1-selective agents. Potential confounding factors in our case report include the controlled hospital environment, the absence of the patient's mother, and the therapeutic benefit of interaction with hospital staff.

## CONCLUSIONS

Although the autonomic hyperactivity hypothesis of aggression in ASD partially explains the behavior of our patient, aggression likely stems from multiple sources beyond just peripheral autonomic arousal. The rapid improvement with propranolol at a fairly low dose suggests that a subpopulation of patients may benefit from non-selective beta blockers. As beta blockers have hemodynamic side effects that include hypotension and bradycardia, clinicians

### KEY POINTS/CLINICAL PEARLS

- Though autism spectrum disorder (ASD) is primarily a disorder of language and social functioning, there may also be significant autonomic dysfunction that could contribute to aggression and impulsivity often seen in the disorder.
- Beta-adrenergic blocking agents have been shown to reduce aggression in patients with traumatic brain injury and adult-onset neuropsychiatric disorders, but evidence is still limited in patients with ASD.
- The non-selective beta-blockers propranolol and nadolol may significantly alleviate aggression, echolalia, and vital sign derangements in autistic patients; it is unknown whether β1-selective antagonists would have similar effects.

should record baseline vitals and monitor for orthostasis, dizziness, and syncope. Overall, beta blockers may serve as an important therapy for aggression but should not replace a multimodal interventional plan that encompasses pharmacology, psychotherapy, and social support. It will be beneficial to validate the utility of propranolol and other beta blockers for ASD in future randomized controlled trials.

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CASE REPORT

# Elopement in Children With Autism Spectrum Disorder

Veeraraghavan J. Iyer, M.B.B.S., M.D.

Children with autism spectrum disorder (ASD) fixate longer on cartoon characters and show greater emotion recognition to cartoons when compared to real faces (1). Observational studies have shown some differences in perception of cartoon faces in children with ASD compared with their typically functioning peers (1–4). Face and emotion processing is a function of social functioning. Impairment in social functioning may predict elopement in children with ASD (5). Elopement is defined in the present article as an escape from the caretaker's confines (e.g., home). Elopement rates are estimated to be nearly four times higher in children with ASD when compared with their siblings who do not have such a diagnosis (5). We investigated different strategies in curbing elopement tendencies in children with ASD.

## METHOD

We describe two children with ASD who were diagnosed by mental health practitioners using DSM-IV criteria. The diagnoses were corroborated in the current visits using the Modified Checklist for Autism in Toddlers-Revised (M-CHAT-R) online scoring system. Their degree of social impairment was estimated using a non-standardized version of the Social Responsiveness Scale (SRS), with a 5-point Likert scale. One question for each of the following criteria was given: awareness, cognition, communication, mannerisms, and motivations. A literature search was conducted to investigate cartoon perception and facial recognition differences in children with ASD. Additionally, we reviewed certain behavioral strategies to decrease elopement in children with ASD.

## CASE 1

"Joseph" is a 13-year-old middle-class Hispanic boy, previously diagnosed with ASD at the age of 7, who was brought into the emergency department by police when found loitering in the streets. He was verbally provocative and violently swinging his hands at the police. As a result, he had to be restrained prior to arrival. In the emergency department, he became more aggravated upon the sight of his parents and had to be restrained for a second time. The M-CHAT-R questionnaire was administered to support the diagnosis of ASD. Upon evaluation, he believed that his parents were trying to harm him by casting a curse upon him. He repeatedly referred to himself as a hero from certain movies such as Percy Jackson. He compared his parents to villainous characters such as "Medusa the evil witch." A week prior to the current visit, he was brought to the emergency department for elopement from similar beliefs. He had been harboring feelings of paranoia against his parents for the past 3 months. Upon administering the SRS, he scored 16/25, suggesting a high degree of social impairment for questions of social communication, motivation, and autistic mannerisms.

## CASE 2

"Chad" is a 15-year-old middle-class Caucasian youth, previously diagnosed with ASD, who was brought to the emergency department by police for wandering suspiciously around a mall parking lot and traversing up and down the elevator persistently. In the emergency department, he was chanting out phrases from his favorite television cartoon shows and was clinically dehydrated from his long march on foot. This was the second time he eloped from home in two months. His mother had placed a tracking device on his wrist after the first elopement. The police had difficulty tracking him, owing to range of signal problems. Upon administration of the SRS, he scored 15/25.

## DISCUSSION

A retrospective study conducted by Anderson et al. (5) estimated that about 48% of children with ASD elope from a safe environment. The study also reported that children who were more likely to elope had lower intellectual, communication, and developmental quotients of functioning. Another study reported that more than a third of children with ASD who eloped were never or rarely able to communicate their name, address, or phone number (6). A National Autism Association initiative called "Be REDy" concluded that 36% of children with ASD who eloped nearly drowned and a small number exposed themselves to potentially fatal road traffic accidents (7). Therefore, elopement is a serious behavioral quandary.

Early developmental studies in 8-month and 5-month old infants have shown that typically developing infants tend to look longer at photographed real faces than cartoon faces displaying different emotions, suggesting that they respond more to emotion changes in real faces (2, 8). Rosset et al. showed that children with ASD did not fixate on real face photographs for as long as children without ASD (1, 3). Interestingly, children with ASD fixated on cartoon faces as long as children without ASD, suggesting that the former give preference to cartoon faces over real faces. Another study utilizing brain event-related potentials showed that children with ASD were drawn equally toward photographs

of objects and those of familiar faces (9). In contrast, children without ASD focused longer on face photographs than on object photographs. This suggests that real faces do not have the same social significance for children with ASD as they do for typically developing children (9). This "non preference" for real faces in children with ASD may contribute to difficulties in social perception and interaction (1–3, 4, 9).

Garner (10) studied a graduated levels program in a 19-year-old male with ASD. This study employed means such as praising the act of asking permission to go out, providing more access to cartoons as a reward for non-elopement, curtailing elopement with time-outs, and telling the subject to "stop" when he attempted to elope. This was achieved over gradual increments in the period of supervision. Depending upon elopement attempts over time, more reward or less punishment was administered, hence being called a "graduated levels program." Blocking or physically obstructing a child every time he or she eloped was another intervention reported in one case study (11). Blocking showed a decrease in elopement tendency when compared with rewarding non-elopement with more cartoon time alone. Lang et al. (12) showed that giving verbal and physical attention to the child resulted in reduced elopement when compared with physical redirection (blocking) or access to favorite cartoons alone.

Some of the latest interventions studied are the role of robots in behavior modeling. Robots are capable of humanoid activities without the emotional or contextual component. In a systematic review conducted by Diehl et al. (13), two studies showed promising future applications (14, 15). The first study examined the effects of prosocial behavior when interacting with robots. Pushing buttons on the robot was used as a function of destructive behavior in children with ASD. The more the child pushed buttons on the robot, the less interactive the robot became, with the child displaying negative reinforcement, thus, modulating social behavior using robots. The second study examined robot interactions with children during a game of basketball. The robot varied its skill of playing depending upon the ability of the child to interact and play, thus encouraging children to participate in shared play. Hence, in children with ASD who may give preference for objects over real faces (9), robotic intervention studies may be an innovative approach, which requires thorough evaluation over a larger scale.

The role of virtual reality technologies represents a growing area of research within the field of autism (16). Virtual reality technologies represent a simulation of real-world training environments based on computer graphics. These can be useful in developing interactive programs that involve role playing and cartoons. This may be particularly helpful in children with ASD who give social preference to cartoons.

The limitations in the studies by Garner et al., Call et al., and Lang et al. were the presence of only a single participant, which makes generalization difficult (10–12). Robot-based studies and the virtual reality technology study were limited by small sample sizes and selection bias (14–16). Children with ASD involved in the study had a higher level of functioning.

## KEY POINTS/CLINICAL PEARLS

- Behavioral interventions like blocking and verbal redirection may be promising therapies to prevent elopement in autism spectrum disorder..
- Involvement of caretakers and teachers in such behavioral interventions is important.
- Innovative technological interventions such as virtual reality technologies and robotic technology are worth further exploring as potential modalities for treating behaviors in patients with autism spectrum disorder.

## CONCLUSIONS

There is evidence that children with ASD give preference to cartoons and objects over real faces. This observation may support the use of cartoons, robots and virtual reality technology to develop social skills, behaviour modulation, and thus control elopement tendencies. Studies that showed a decrease in elopement incorporated graduated levels programs, blocking, rewarding, robots, and virtual reality technology. Such interventions need further investigation over a larger scale to better establish their role in decreasing elopement.

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CASE REPORT

# Neuropsychiatric Symptoms in the Pediatric Population After Administration of Oseltamivir

Shariq F. Haque, M.D., Sobia Nizami, M.D.

Oseltamivir is a neuraminidase inhibitor used to treat influenza infection, which acts by inhibiting the release of replicated virus from infected cells. While shown to cause symptom relief in adults if taken within 48 hours of symptom onset, its use has shown no significant reduction in hospitalization rates or complications from infection in hospitalized patients (1). Despite demonstration of limited benefit, the drug is widely used, with a total of 48 million patients receiving prescriptions for oseltamivir worldwide since 2006 (1). Approximately 10% of the drug penetrates the blood-brain barrier (1), which allows for potential neuropsychiatric side effects (2). Neuropsychiatric sequelae of oseltamivir have been well documented in the medical literature (3). The Food and Drug Administration added a warning about oseltamivir use and neuropsychiatric adverse events. The majority of these adverse events have been observed to have occurred in the pediatric population. Neuropsychiatric adverse events include delirium, disturbances in consciousness, perceptual changes, delusions, tremors, anxiety symptoms, seizure disorders, parasomnias, and apocrine and eccrine gland disorders (4). Neuropsychiatric adverse events are delineated into sudden onset, which starts within 24 hours after administration, and delayed onset, which begins after 24 hours. Sudden-onset adverse events include sensory changes, impairments in cognition, and abnormal behaviors, whereas delayed-onset events mostly consist of abnormal behaviors (2). Japan contraindicated its use among individuals aged 10 to 19 due to concerns of abnormal behaviors (1). We describe a case of delayed-onset psychiatric manifestations of oseltamivir administration in and 8-year-old girl.

## CASE

"Sally" is an 8-year-old girl who presented to the emergency department with the complaint of auditory hallucinations for the past 2 weeks. Prior to the onset of auditory hallucinations, the patient was started on and completed a course of oral oseltamivir (60 mg b.i.d. for 5 days). She had tested positive for influenza A 2 weeks prior to using the rapid screen. After finishing the course of oseltamivir, she began endorsing auditory hallucinations. She described two voices, one sounding like her mother's, the other a male's voice. She further described the voices as, "In my head, yelling and screaming."

The patient was born by caesarean section at 39 weeks gestation. She had normal milestones and no reported history of trauma or neglect. She was in regular schooling, with only recent reports from teachers of the patient endorsing auditory hallucinations. She had neither a past psychiatric history nor any family history of psychiatric conditions. Mental status examination revealed a typically developing 8-year-old female. No visual hallucinations were described; there were no mood symptoms; no delusions were elicited; and the patient did not complain of any anxiety. Her affect was moderately constricted, and her thought process was logical, with some thought blocking. The child did at times appear to be internally preoccupied. Complete blood count, metabolic profile, MRI scan, and continuous video EEG were unremarkable. Approximately 48 hours after admission, the patient stopped endorsing any auditory hallucinations, and she was subsequently discharged with outpatient follow-up. She did not receive any psychotropic medications and denied any psychiatric symptoms on outpatient follow-up.

## DISCUSSION

This above case describes delayed-onset psychiatric manifestations of oseltamivir administration in the pediatric population, as the hallucinations appeared after the completion of the course of oseltamivir. Oseltamivir appears to have a net excitatory effect in the CNS (5). This is possibly attributed to sialylation (addition of sialic acid groups) of serum glycolipids, which in turn stimulates D2 receptors (2, 6). Sialylation of serum glycolipids causes an increase of D2 receptor activity (dopamine neurons possess glycoside receptors that are activated in the presence of sialylated glycolipids) (6), which has been associated with enhanced behaviors in mice (6). In one study, mice exposed to either dopamine agonists or oseltamivir were more likely to jump down from a 20-cm high platform (6). Hiasa et al. (7) reported that if oseltamivir was administered to the intraventricular system in mice, this significantly increased spontaneous behavior, such as sniffing, jumping, rearing, turning, and walking. Another possible mechanism, postulated by Morimoto et al. (8), implicated limbic GABAergic dysfunction. The authors reported a case of a 15-year-old patient with acute-onset neuropsychiatric effects after oseltamivir administration, which responded well to diazepam and midazolam (8). The researchers report reduced GABA-A activity in the patient's right medial temporal lobe on SPECT scan. The clinical picture resembled autoimmune limbic encephalitis in the absence of abnormal CSF or EEG findings. Susceptibility of the pediatric population to these effects

### KEY POINTS/CLINICAL PEARLS

- Neuropsychiatric side effects of oseltamivir include delirium, disturbances in consciousness, perceptual changes, delusions, tremors, anxiety symptoms, seizure disorders, parasomnias, and apocrine and eccrine gland disorders.
- Researchers have found increased propensity for mice to jump from 20-cm high platforms when given pure dopamine agonists or oseltamivir.
- Ten percent of oseltamivir enters the blood-brain barrier where it sialylates certain glycolipids, causing increased activation of D2 receptors; this combined with other mechanisms may dysregulate the balance of excitation and inhibition, causing a net excitation, which is postulated to cause abnormal behaviors.
- Reduced GABA-A activity in the medial temporal lobe was found in one case of suspected oseltamivir-induced neuropsychiatric symptoms.

could be attributed to lower amounts of P-glycoprotein, which is present in the blood-brain barrier and is known to limit oseltamivir uptake (9).

## CONCLUSIONS

Oseltamivir is a commonly used medication for the treatment of influenza. Numerous case studies and clinical trials have indicated that it may cause neuropsychiatric side effects in young children, particularly due to its neuroexcitatory properties. Stimulation of D2 receptors and dysfunction of GABA-A receptor shave been implicated. Given that the medication is only shown to garner symptom relief, the risks versus benefits of treatment must be weighed. Children receiving oseltamivir should be monitored for neuropsychiatric side effects.

Dr. Haque is a third-year psychiatry resident at Rutgers New Jersey Medical School, Newark, N.J. Dr. Nizami is a third-year resident in internal medicine at Rutgers New Jersey Medical School.

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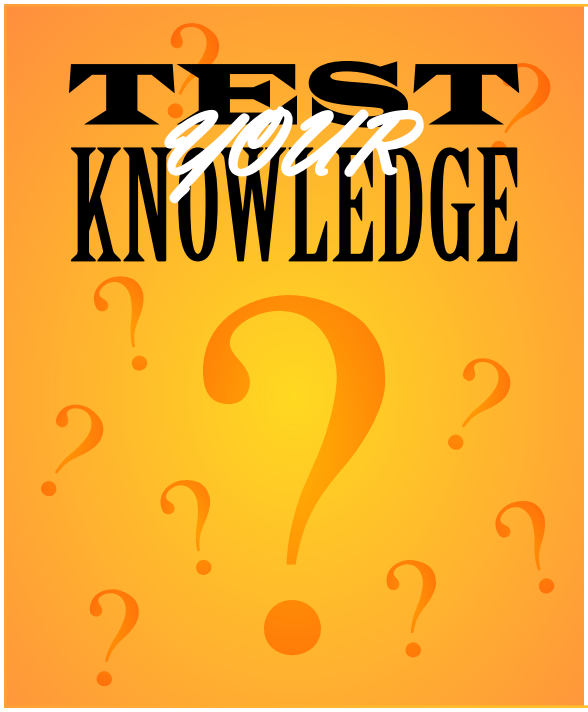


### TEST YOUR KNOWLEDGE HAS MOVED

Our Test Your Knowledge feature, in preparation for the PRITE and ABPN Board examinations, has moved to our Twitter (www.twitter.com/AJP_ResJournal) and Facebook (www.facebook.com/AJPResidentsJournal) pages.

We are currently seeking residents who are interested in submitting Board-style questions to appear in the Test Your Knowledge feature. Selected residents will receive acknowledgment for their questions.

Submissions should include the following:

1. Two to three Board review-style questions with four to five answer choices.
2. Answers should be complete and include detailed explanations with references from pertinent peer-reviewed journals, textbooks, or reference manuals.

**Please direct all inquiries to Rachel Katz, M.D., Senior Deputy Editor (rachel.katz@yale.edu).*

# Call for Applications to Join the 2017 Editorial Board

The *American Journal of Psychiatry—Residents' Journal* is now accepting applications to join the 2017–2018 Editorial Board for the following positions:

## SENIOR DEPUTY EDITOR POSITION 2017

**Job Description/Responsibilities**

- Frequent correspondence with AJP-Residents' Journal Editorial Board and AJP professional editorial staff, including a monthly conference call.
- Frequent correspondence with authors.
- Peer review manuscripts on a weekly basis.
- Make decisions regarding manuscript acceptance.
- Work with AJP editorial staff to prepare accepted manuscripts for publication to ensure clarity, conciseness, and conformity with AJP style guidelines.
- Coordinate selection of book review authors and distribution of books with AJP professional editorial staff.
- Recruit authors and guest editors for the journal.
- Manage the *Test Your Knowledge* questions and work closely with authors in developing Board-style review questions for the *Test Your Knowledge* section.
- Collaborate with the Editor-in-Chief in selecting the 2018 Senior Deputy Editor, Deputy Editor, and Associate Editors.
- Attend and present at the APA Annual Meeting.
- Commitment averages 10–15 hours per week.

**Requirements**

- Must be an APA resident-fellow member.
- Must be starting as a PGY-3 in July 2017, or a PGY-4 in July 2017 with plans to enter an ACGME fellowship in July 2018.
- Must be in a U.S. residency program.

Selected candidate will be considered for a 2-year position, including advancement to Editor-in-Chief.

## DEPUTY EDITOR POSITION 2017

**Job Description/Responsibilities**

- Frequent correspondence with Residents' Journal Editorial Board and AJP professional editorial staff, including a monthly conference call.
- Frequent correspondence with authors.
- Peer review manuscripts on a weekly basis.
- Make decisions regarding manuscript acceptance.
- Work with AJP editorial staff to prepare accepted manuscripts for publication to ensure clarity, conciseness, and conformity with AJP style guidelines.
- Prepare a monthly *Residents' Resources* section for the Journal that highlights upcoming national opportunities for medical students and trainees.
- Recruit authors and guest editors for the journal.
- Collaborate with the Editor-in-Chief in selecting the 2018 Senior Deputy Editor, and Associate Editors.
- Attend and present at the APA Annual Meeting.
- Commitment averages 10 hours per week.

**Requirements**

- Must be an APA resident-fellow member.
- Must be a PGY-2, PGY-3, or PGY-4 resident starting in July 2017, or a fellow in an ACGME fellowship in July 2017.
- Must be in a U.S. residency program or fellowship.

This is a 1-year position only, with no automatic advancement to the Senior Deputy Editor position in 2018. If the selected candidate is interested in serving as Senior Deputy Editor in 2018, he or she would need to formally apply for the position at that time.

## ASSOCIATE EDITOR POSITIONS 2017

(two positions available)

**Job Description/Responsibilities**

- Peer review manuscripts on a weekly basis.
- Make decisions regarding manuscript acceptance.
- Recruit authors and guest editors for the journal.
- Collaborate with the Senior Deputy Editor, Deputy Editor, and Editor-in-Chief to develop innovative ideas for the Journal.
- Attend and present at the APA Annual Meeting.
- Commitment averages 5 hours per week.

**Requirements**

- Must be an APA resident-fellow member.
- Must be a PGY-2, PGY-3, or PGY-4 resident in July 2017, or a fellow in an ACGME fellowship in July 2017.
- Must be in a U.S. residency program or fellowship.

This is a 1-year position only, with no automatic advancement to the Deputy Editor or Senior Deputy Editor position in 2018. If the selected candidate is interested in serving as Deputy Editor or Senior Deputy Editor in 2018, he or she would need to formally apply for the position at that time.

## MEDIA EDITOR POSITION 2017

(one position available)

**Job Description/Responsibilities**

- Manage our Twitter and Facebook accounts
- Oversee podcasts
- We are open to many suggestions within reason
- Collaborate with the associate editors to decide on content
- Collaborate with Senior Deputy Editor, Deputy Editor, and Editor-in-Chief to develop innovative ideas for the Journal.
- Attend and present at the APA Annual Meeting.
- Commitment averages 5 hours per week.

**Requirements**

- Must be an APA resident-fellow member.
- Must be an upcoming PGY-2, PGY-3, or PGY-4 resident in July 2017, or a fellow in an ACGME fellowship in July 2017.
- Must be in a U.S. residency program or fellowship.

This is a 1-year position only, with no automatic advancement to the Deputy Editor or Senior Deputy Editor position in 2018. If the selected candidate is interested in serving as Deputy Editor or Senior Deputy Editor in 2018, he or she would need to formally apply for the position at that time.

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**For all positions, applicants should e-mail a CV and personal statement of up to 750 words describing their reasons for applying, as well as any ideas for journal development to Rachel.Katz@yale.edu.**

**The deadline for applications is 3/31/2017.**

# Residents' Resources

Here we highlight upcoming national opportunities for medical students and trainees to be recognized for their hard work, dedication, and scholarship.

**To contribute to the Residents' Resources feature, contact Oliver Glass, M.D., Deputy Editor (glassol@ecu.edu).*

## MARCH DEADLINES

| Fellowship/Award, Organization, and Deadline | Brief Description and Eligibility | Contact and Website |
|---|---|---|
| American Academy of Child and Adolescent Psychiatry (AACAP) Pilot Research Award for Child Psychiatry Residents and Junior Faculty<br><br>AACAP<br><br>**Deadline: March 30, 2017** | Offers $15,000 for child psychiatry residents and junior faculty who have an interest in beginning a career in child and adolescent psychiatry research. Recipients have the opportunity to submit a poster presentation on their research for AACAP's 64th Annual Meeting in Washington, DC, 2017. The award also includes the cost of attending the AACAP Annual meeting for 5 days.<br>• Enrolled in a child psychiatry residency or fellowship or have a faculty appointment in an accredited medical school but no more than 2 years of experience following graduation from training. Candidates must not have any previous significant, individual research funding in the field of child and adolescent mental health.<br>• AACAP member | Department of Research, Training, and Education<br><br>E-mail: research@aacap.org<br>Phone: (202) 587-9664<br><br>http://www.aacap.org/AACAP/Awards/Resident_and_ECP_Awards/Pilot_Research_Award_Child_Psychiatry_Residents_Junior_Faculty.aspx |
| AACAP Pilot Research Award, supported by Pfizer, Inc.<br><br>AACAP, Supported by Pfizer<br><br>**Deadline: March 30, 2017** | Offers $15,000 for general psychiatry residents who have an interest in beginning a career in child and adolescent mental health research. Recipients have the opportunity to submit a poster presentation on their research for the AACAP 64th Annual Meeting in Washington, DC, 2017. The award also includes the cost of attending the AACAP Annual Meeting for 5 days<br>• Candidates must be enrolled in a general psychiatry residency. Candidates must not have any previous significant, individual research funding in the field of child and adolescent mental health.<br>• AACAP member. | Department of Research, Training and Education<br><br>E-mail: research@aacap.org<br>Phone: (202) 587-9664<br><br>http://www.aacap.org/aacap/Awards/Resident_and_ECP_Awards/AACAP_Pilot_Research_Award.aspx |
| AACAP Pilot Research Award for Learning Disabilities for Child Psychiatry Residents and Junior Faculty<br><br>AACAP, Supported by the Elaine Schlosser Lewis Fund<br><br>**Deadline: March 30, 2017** | Offers $15,000 for child and adolescent psychiatry residents and junior faculty who have an interest in beginning a career in child and adolescent mental health research. The recipient has the opportunity to submit a poster presentation on his or her research for the 64th Annual Meeting in Washington, DC, 2017.<br>• Enrolled in a child psychiatry residency or fellowship or have a faculty appointment in an accredited medical school but no more than 2 years of experience following graduation from training.<br>• Candidates must not have any previous significant, individual research funding in the field of child and adolescent mental health.<br>• AACAP member | Department of Research, Training, and Education<br><br>E-mail: research@aacap.org<br>Phone: (202) 587-9664<br><br>http://www.aacap.org/AACAP/Awards/Resident_and_ECP_Awards/AACAP_Pilot_Research_Award_for_Learning_Disabilities.aspx |
| American Psychiatric Association (APA) Resident Recognition Award<br><br>APA<br><br>**Deadline: March 31, 2017** | The Resident Recognition Award is presented annually to outstanding psychiatry residents or fellows from each department or institution who exemplifies one or more APA values. Multiple awards are given each year.<br>Psychiatry residents or fellows who:<br>• Are APA members;<br>• Are in good standing in their general psychiatry or fellowship program. | Claire Van Wagner<br>E-mail: cvanwagner@psych.org<br><br>https://www.psychiatry.org/psychiatrists/awards-leadership-opportunities/awards/resident-recognition-award |

# Author Information for *The Residents' Journal* Submissions



***The Residents' Journal*** accepts manuscripts authored by medical students, resident physicians, and fellows; attending physicians and other members of faculty cannot be included as authors.

To submit a manuscript, please visit http://mc.manuscriptcentral.com/appi-ajp, and select a manuscript type for AJP Residents' Journal.

1. **Commentary:** Generally includes descriptions of recent events, opinion pieces, or narratives. Limited to 500 words and five references.
2. **History of Psychiatry:** Provides a historical perspective on a topic relevant to psychiatry. Limited to 500 words and five references.
3. **Treatment in Psychiatry:** This article type begins with a brief, common clinical vignette and involves a description of the evaluation and management of a clinical scenario that house officers frequently encounter. This article type should also include 2–4 multiple choice questions based on the article's content. Limited to 1,500 words, 15 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
4. **Clinical Case Conference:** A presentation and discussion of an unusual clinical event. Limited to 1,250 words, 10 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
5. **Original Research:** Reports of novel observations and research. Limited to 1,250 words, 10 references, and two figures. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
6. **Review Article:** A clinically relevant review focused on educating the resident physician. Limited to 1,500 words, 20 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
7. **Drug Review:** A review of a pharmacological agent that highlights mechanism of action, efficacy, side-effects and drug-interactions. Limited to 1,500 words, 20 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
8. **Perspectives in Global Mental Health:** This article type should begin with a representative case or study on psychiatric health delivery internationally, rooted in scholarly projects that involve travel outside of the United States; a discussion of clinical issues and future directions for research or scholarly work should follow. Limited to 1,500 words and 20 references.
9. **Arts and Culture:** Creative, nonfiction pieces that represent the introspections of authors generally informed by a patient encounter, an unexpected cause of personal reflection and/or growth, or elements of personal experience in relation to one's culture that are relevant to the field of psychiatry. Limited to 500 words.
10. **Letters to the Editor:** Limited to 250 words (including 3 references) and three authors. Comments on articles published in the *Residents' Journal* will be considered for publication if received within 1 month of publication of the original article.
11. **Book and Movie Forum:** Book and movie reviews with a focus on their relevance to the field of psychiatry. Limited to 500 words and 3 references.

# Upcoming Themes

If you have a submission related to the themes shown at right, contact the Section Editor listed below the topic. ***Please note that we will consider articles outside of the theme.***

If you are interested in serving as a **Guest Section Editor** for the *Residents' Journal*, please send your CV, and include your ideas for topics, to Rachel Katz, M.D., Senior Deputy Editor (rachel.katz@yale.edu).

**Mental Health of Healthcare Providers**
Charles Johnson, M.D., charles.a.johnson@ucdenver.edu

**LGBT Mental Health**
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**War, Terror, and Psychopathology**
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