Challenges in the Psychopharmacological Management of Very Early-Onset Schizophrenia and Anxiety

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Chief Complaint and Presenting Problem

A. WAS A 13-YEAR-OLD HAITIAN RIGHT-HANDED BOY in eighth grade in a special education school who carried a diagnosis of having autism spectrum disorder (ASD) referred for outpatient evaluation of increasing impairment in school functioning.

History of Present Illness

A.'s mother became concerned about him early in life. Mother reported that A. had significant delays in language acquisition. A. reportedly did not speak until age 6 years despite normal hearing and early speech and language intervention. Between ages 3 and 4 years, he was diagnosed with ASD because of verbal and nonverbal communication deficits, lack of reciprocal social behavior, odd behavior, perseveration, and restricted interests. As he entered school, significant separation anxiety occurred. Attention-deficit/hyperactivity disorder (ADHD) symptoms, including inattention and hyperactivity/impulsivity, were noted in early elementary school. As his school adjustment worsened, mother repeatedly transferred A. to many different schools in an attempt to find an academic situation that would meet his needs. Mother became convinced that some unidentified traumatic experience at school was the reason for A.'s poor school adjustment, although there was no evidence in his history of any traumatic events. Because of mother's focus on trauma, neither psychological educational testing nor treatment for ADHD and anxiety was pursued.

By fifth grade, A. began exhibiting anxiety in almost all areas of daily life. Symptoms included separation fears, generalized anxiety about mother's well-being, fears of speaking in school, and nighttime fears. Mother continued to believe that this was due to some unexplained trauma that A. had experienced. At school, A. continued to have poor adjustment with prominent symptoms of anxiety and ADHD and frequent disruptive behaviors. At home, he isolated himself in his room, watching television. He began to display inappropriate and incongruent affect, frequently laughing and talking to himself along with episodes of irritability and inappropriate display of anger. A. frequently disrupted his classroom with episodes of aggressive behavior and incongruent laughter.

Psychotherapy was started, but discontinued after only several visits with the therapist because mother felt it was not helpful. A. was transferred to a special needs school, but became selectively mute in the classroom and began to refuse to attend school. An

additional school psychological evaluation supported a diagnosis of ASD. At this time, mother sought child psychiatric evaluation.

Psychiatric History

A. had never been psychiatrically hospitalized. Pediatric evaluation at age 4 years led to a diagnosis of autism as a result of A.'s developmental delays, odd behavior, and social isolation, supported by a psychological evaluation at age 11 years. A. had no history of substance abuse. A previous outpatient physician had prescribed aripiprazole 2 mg at bedtime (HS) without significant benefit when A. was age 11 years.

Developmental History

A. was the product of an uneventful pregnancy and uncomplicated delivery. There was no prenatal use of alcohol, tobacco, or narcotics. Fine motor delays were noted, but A. was not delayed in walking. Significant delays in speech and language were present. Significant cognitive delays were documented by a full-scale intelligence quotient (IQ) of 66.

Educational History

A. received early speech and language services. He received continuous special educational services beginning in kindergarten.

Social and Family History

A. lived with his biological mother and 18-year-old brother. The family was Haitian American and spoke French and English at home. Mother described herself as having a speech delay, but was able to complete high school. Mother reported no psychiatric history in first- and second-degree maternal relatives.

A.'s brother was healthy.

Biological father had never been involved in A.'s care. He resided overseas and had no contact with A. Little is known about father's psychiatric or family history.

Mother is a single parent working at minimum wage and is the sole source of support for the family.

Medical History

A. was healthy and had no known drug allergies. Hearing and vision screens were normal. On initial physical evaluation,

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blood pressure was 106/67 mmHg, pulse was 81 bpm, height was 157.5 cm, and weight 66.1 kg. A. was obese with a body-mass index >95% for gender and age.

A screening pediatric evaluation completed within 1 month of psychiatric evaluation was normal except for obesity. Laboratory screening was normal for complete blood count (CBC) with differential, platelet count, liver function tests, fasting glucose, thyroid-stimulating hormone, free thyroxine, electrolytes, and blood urea nitrogen (BUN) and creatinine. Triglycerides were elevated. A screening electrocardiogram showed normal sinus rhythm.

Mental Status Examination

On initial interview, A. presented in casual dress, slightly disheveled, and with poor hygiene. There were multiple active and healing lesions on all extremities from his continued scratching. He was alert and oddly related with poor eye contact. He kept the hoodie of his sweatshirt up, covering his face until prompted by mother. He did not exhibit any facial or cranial dysmorphism. He did not respond reciprocally or appropriately to social cues. He interacted minimally with his mother and the examiner, but did comply with instructions. He only uttered a word or two, spoken at a very low volume and in a monotonous voice. His affect alternated between blunt and incongruent. He frequently laughed out loud, his eye gaze tracked laterally, his eyelids flickered bilaterally, and he appeared internally preoccupied. At other times, he acted silly and his behavior became disorganized. His attention span and concentration were poor. Because he did not speak, the presence of auditory or other hallucinations or delusions could not be determined by interview. To the extent that his thought process could be elucidated, he appeared tangential in his thinking. He demonstrated good impulse control during the interview. He did not appear depressed or manic. No suicidal, homicidal, or high-risk ideation or intent was endorsed. He was not oriented to time, but was oriented to person and place. His cognition appeared delayed relative to his chronological age. Judgment was poor and his insight was very limited.

Additional Evaluation

A clinician-administered Positive and Negative Symptom Scale (PANSS) was completed with a total score of 100, a positive symptom scale of 22, a negative symptom scale of 29, and a general psychopathology scale of 49 (Suzuki 2011). Symptoms appeared minimized and underreported on parent-completed rating scales assessing anxiety, ADHD, and generalized psychopathology. Although mother appeared to understand how to complete these rating scales, she denied that anxiety, attentional deficits, hyperactivity-impulsivity, and depression were problematic for her son.

A Barnes Akathisia Scale and Simpson-Angus Extrapyramidal Scale were within normal limits. Because of involuntary lateral eye movements, A.'s score on the Abnormal Involuntary Movement Scale (AIMS) was 3 (abnormal).

Because of concern that his presentation might be explained, in part, by absence seizures, A. was referred to pediatric neurology. Neurological consultation found no acute or chronic neurological disease and supported a psychiatric etiology for A.'s presentation. Specifically, pediatric neurology did not find that A.'s lateral eye movements were secondary to a movement disorder, such as a medication dystonic reaction, or to a tic disorder. Neurology speculated that A.'s gaze aversion might be related to his response to internal stimuli such as a hallucination.

A screening electroencephalogram (EEG) performed in the awake, drowsy, and sleep states with activating procedures, including hyperventilation and photic stimulation, was normal.

Treatment Course

A.'s treatment was complicated by mother's insistence that his symptoms were entirely caused by a school-related traumatic event and her reluctance to accept other explanations for his symptoms and impaired functioning. Despite multiple and continued efforts by clinicians to educate mother about the nature of A.'s psychotic and anxiety symptoms and the need for a multimodal treatment plan, including psychopharmacology, she remained reluctant to agree to psychopharmacological treatment with antipsychotic and anxiolytic medications. Only consenting to a trial of low-dose antipsychotics, A.'s aripiprazole was initiated at 2.5 mg HS and then titrated to 5 mg HS.

A. continued to have symptoms of separation anxiety, nighttime fears, and generalized worries relating to school expectations and social interactions. To treat symptoms of severe anxiety, sertraline was initiated and titrated to 50 mg/day. Low-dose sertraline was effective in diminishing the severity of A.'s anxiety symptoms without exacerbating his psychosis, but mother refused to allow a higher dose. She then stopped the medication, fearing that A.'s episodic irritability was a side effect. Anxiety symptoms returned and mother agreed to restart the sertraline 50 mg/day. A.'s anxiety symptoms promptly improved. Mother again discontinued the sertraline because of concerns that the medication exacerbated A.'s scratching. She agreed to a switch to escitalopram 5 mg, and anxiety symptoms subsequently improved.

A. remained in psychiatric treatment at an ambulatory level of care. He continued in special education in a separate special needs school with a high teacher-to-student ratio, a one-to-one aide in the classroom, behavioral consultation to the classroom, and educational curricula appropriate to his mental age. He lived at home and continued to frequently isolate himself in his room. He had no friends outside of school acquaintances. Mother slowly began to recognize the need for medication as part of his multidisciplinary treatment plan. A.'s irritability and aggressive outbursts improved on aripiprazole 5 mg in combination with sertraline 50 mg daily. After 8 weeks on this regimen, a follow-up PANSS revealed a total score of 73 (27% improvement), a positive symptom scale of 12 (45% improvement), a negative symptom scale of 28 (3% improvement), and a general psychopathology scale of 33 (33% improvement) (Suzuki 2011). His lateral eye movements diminished in frequency as his psychotic symptoms improved, his eye contact improved, and his incongruent laughter diminished in frequency and severity.

Brief Formulation

In summary, A. is a 13-year-old Haitian American boy with a prior diagnosis of ASD, intellectual disability, and a developmental history characterized by attention deficits, impulsive behavior, and neuromotor, speech and language delays referred for a multiyear history of gradual onset of odd disorganized behavior, social isolation, incongruent affect, and episodic irritability. He appeared to respond to internal stimuli with inappropriate laughter, silly disorganized behaviors, and sudden episodic lateral gaze movements. His difficulty engaging verbally with his clinicians prevented a clear understanding of whether auditory or visual hallucinations were present. His symptoms were not better explained by a neurological or medical disorder or a substance-induced psychotic disorder. Psychiatric evaluation did not support an affective

psychosis such as mania or psychotic depression. His symptoms suggested the gradual emergence of a primary, very early-onset schizophrenia-spectrum disorder (VEOSSD); however, in the absence of verified hallucinations or delusions, a diagnosis of schizophrenia could not be definitively made. A.'s primary psychotic diagnosis was complicated by comorbid ASD, cognitive delays, severe social phobia, selective mutism, and generalized anxiety disorder that further impaired his daily functioning. Since his scratching symptoms were recurrent, repetitive, resulted in lesions, and were not responsive to repeated attempts to stop, and because his scratching did not appear to be a result of psychosis or ASD, he met criteria for excoriation (skin picking) disorder.

From a biological perspective, impairments in social cognitive development (e.g., early ASD diagnosis) and delays in neuromotor, cognitive, and language development increased A.'s risk of developing schizophrenic-spectrum disorders by puberty. His early-onset and persistent developmental deficits suggested pan-developmental impairment known to increase risk for early-onset psychotic symptoms and schizophrenic-spectrum disorders (Cannon et al. 2002; McNeil et al. 2011).

From a psychological perspective, A.'s psychiatric evaluation and treatment were complicated by mother's belief that A.'s symptoms were solely due to a single school-related traumatic experience. As a result, she experienced difficulties recognizing and accepting his psychiatric diagnoses and the need for a multidisciplinary treatment plan. From a social perspective, mother was a single working parent raising two children by herself. A lack of resources was likely a significant social stressor for the family.

Diagnosis

Axis I: Unspecified schizophrenia-spectrum and other psychotic disorder

ASD

Intellectual disability (mild)

Social anxiety disorder

Generalized anxiety disorder

Excoriation (skin picking) disorder

ADHD, past diagnosis

Axis II: No diagnosis

Axis III: Obesity

Axis IV: Educational problems

Economic problems (single mother working at minimal wage)

Problems with social environment

Axis V: Global assessment of functioning score: 30

Discussion

Our case illustrates several important challenges in the evaluation and management of VEOSSD in children. First, A.'s case illustrates a relationship between pervasive developmental disorder and the onset of psychosis in later childhood. Second, VEOSS is often difficult to treat, as positive symptoms tend to respond better to treatment than negative symptoms. Next, given high rates of comorbid psychiatric disorders in VEOSSD, rational combined pharmacotherapy is often indicated in treatment. Finally, our case illustrates the challenges that parents may have in accepting the diagnosis of VEOSSD and how that may affect the child's treatment course.

VEOSSD are defined as nonaffective, nonsubstance-related psychotic disorders with an onset of symptoms before age 13 years. Considered to be a severe and disabling group of psychiatric conditions, onset is usually after age 7 years, positive and negative

symptoms are prominent, and the prognosis is poor (Rapoport et al. 2009). Current models for the development of VEOSSD emphasize neurodevelopmental theory. This theory postulates that abnormal development of the central nervous system during embryological life renders the individual vulnerable to the subsequent development of schizophrenia as development unfolds, generally around puberty (Lieberman et al. 2001; McNeil et al. 2011). The two-hit model of development of schizophrenia postulates that a first hit, such as a genetic predisposition to the disease or *in utero* maternal viral infection, produces an early central nervous system (CNS) vulnerability to schizophrenia. A second hit, probably from environmental factors such as the gonadal steroid surge associated with puberty, may induce the onset of disease (Maynard et al. 2001).

Childhood developmental abnormalities have been described in children with VEOSSD (Fish and Kendler 2005). Longitudinal studies have provided evidence for an early childhood, persistent pan-developmental impairment associated with the onset of schizophrenia-spectrum disorders by age 11 years. Specifically, early childhood onset and developmental persistence of language disorders, cognitive and neuromotor delays may be markers of risk for early-onset psychotic symptoms (Cannon et al. 2002). While we could not find evidence of familial vulnerability to psychotic disorders or any history of at-risk *in utero*, birth, or neonatal events in A.'s history, his early-onset and persistent developmental delays may reflect a vulnerability to VEOSSD that emerged as puberty approached in early adolescence.

A. received a diagnosis of ASD in his preschool years. Emerging evidence suggests a shared neurodevelopmental origin for autism and psychosis. Both are disorders of CNS specialization originating in the embryonic period (de Lacy and King 2013). Data from longitudinal cohort studies find an elevated risk for psychotic disorders by early adolescence in children with ASD (Sullivan et al. 2013), and studies of childhood onset schizophrenia (COS) find that COS is preceded by and comorbid with ASD in 30% to 50% of cases (Rapoport et al. 2009). On the level of molecular biology, genome-wide single-nucleotide polymorphism (SNP) data show that specific SNPs are associated with a range of psychiatric disorders of childhood or adult onset, including ASD, ADHD, bipolar disorder, major depressive disorder, and schizophrenia; and are not specific to single disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013). Thus, A. had a number of neurodevelopmental risk factors for the emergence of VEOSSD.

Negative symptoms, including apathy, blunted affect, energy, and paucity of speech or thought, are common in VEOSSD, occurring in up to 50% of cases (Stentebjerg-Olesen et al. 2016). They are a predictor of poor outcome and respond less well to antipsychotic treatment, compared with positive symptoms such as hallucinations (McClellan et al. 2013). This is consistent with treatment outcomes from our case; positive PANSS symptoms improved by 45% with treatment compared with only 3% for A.'s negative symptoms.

VEOSSD is frequently comorbid with other psychiatric disorders, including posttraumatic stress disorder, ADHD, disruptive behavior disorders, substance use disorders, depression, and anxiety disorders (Stentebjerg-Olesen et al. 2016). In our case, A. had severe comorbid generalized anxiety and social anxiety symptoms. Comorbid anxiety complicated his psychiatric evaluation and required combined pharmacotherapy. In an off-on-off-on trial, sertraline 50 mg/day and then escitalopram 5 mg/day reproducibly improved his anxiety symptoms and overall functioning in combination with aripiprazole 5 mg/day. The addition of a low-dose SSRI did not appear to exacerbate A.'s psychotic symptoms, nor his skin scratching, and was well tolerated. This is consistent with

quantitative reviews of adult schizophrenia clinical trials and qualitative reviews of childhood schizophrenia, which report that SSRI combination with antipsychotics demonstrates small yet beneficial effects on comorbid depressive and anxious symptom severity and does not cause a worsening of psychotic symptoms in individuals with schizophrenia-spectrum disorders (Helfer et al. 2016; Mosheva et al. 2016).

A.'s course of treatment was complicated by his mother's reluctance to accept his diagnosis of unspecified schizophrenia. Despite multiple psychoeducational interventions by multiple clinicians and teachers, mother consistently minimized the severity of A.'s symptoms during evaluation and treatment. Mother remained convinced that if only the right school placement could be found for A., his difficulties would subside. Overly focused on fears of possible medication side effects, mother did not support a dose-optimized antipsychotic medication trial for A.

The transtheoretical model of change describes five stages of change that people move through in changing a given health behavior (Prochaska et al. 1994). These include precontemplation, contemplation, preparation, action, and maintenance. Mother appeared stuck in a precontemplative stage, hoping that with time and the right school placement, A.'s poor prognosis of VEOSSD could be avoided. Her challenges in accepting the severity of A.'s psychiatric diagnosis and need for evidence-based treatment are a reminder that families of children with early-onset schizophrenia-spectrum disorders frequently need considerable support to increase their understanding of the illness, treatment options, and prognosis and to develop strategies to cope with the patient's symptoms (McClellan et al. 2013).

Acknowledgment

The authors acknowledge and thank Melissa Fluehr for her assistance in preparation of this article.

Disclosures

Dr. Connor is a consultant for Rhodes, Supernus, and Shire Pharmaceuticals, Akili Interactive, Inc., and the OAK Group. He receives research support from Shire Pharmaceuticals and National Institute of Mental Health (NIMH). He receives book royalties from the Guildford Press and W. W. Norton. Drs. Mehdi, Zehgeer, and Schweinsburg report no disclosures.

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