JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 23, Number 5, 2013
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Pp. 363–366
DOI: 10.1089/cap.2013.2353

Advanced Pediatric Psychopharmacology

Unremitting Impulsive Aggression in a Child with Childhood Onset Schizophrenia and Pervasive Development Disorder-Not Otherwise Specified: The Role of Stimulants, Atypical Antipsychotics and Mood Stabilizers

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Chief Complaint and Presenting Problem

C is a 7 ½-year-old, right-handed, elementary school student in a special education class, who carries a diagnosis of pervasive developmental disorder-not otherwise specified (PDD-NOS) and childhood onset schizophrenia. C. was initially referred for outpatient psychiatric treatment 1.5 years ago for deteriorating attention and problems with impulse control.

History of Present Illness

Parents report that C. was a normally developing child until age 3 years. They initially became concerned because his play dates usually ended with physical fights, mostly instigated by C. Mother was also concerned about his lack of fluent speech, but he was able to communicate well with gestures and 2–3 word sentences. He was initially taken to a child psychiatrist at age 3. Family reports that he was diagnosed with ''hyperactivity.'' Mother said that at that time he was able to play with peers for only a short while, and had problems when peers refused to cooperate with his rules, sometimes getting physical with them. C. was treated with short-acting methylphenidate 5 to 10 mg daily at age 4 for one year, which was subsequently switched to a long acting version after rebound symptoms occurred.

Parents report that C.'s attention span became even shorter in the following year despite treatment, and he had problems with teachers and peers alike. His most concerning symptom became impulsive aggression toward peers and teachers. It is reported that C. repeatedly hit peers, poked them with pencils, threw heavy objects (including a chair) at others, and bit and spat at others. He also threw objects out of the window, often without a clear precedent. C was switched to long-acting methylphenidate 27 mg daily in the morning, which was subsequently augmented with atomoxetine 25 mg daily at age 5.

Mother reports that C.'s symptoms initially responded to long-acting methylphenidate, but after a few months his aggression and impulsivity further increased. He was maintained on this regimen for almost two years. At his initial presentation to this clinic, C. required parental redirection almost every 10 seconds to stay on task or sit calmly with his mother. He was unable to be alone with his father, and he kicked and bit him without any clear reason. He was not able to do homework (basic drawings, art projects) alone. He did not seem to listen when spoken to directly. Mother reported that C. was very disorganized and left most of his belongings at school when the teacher did not provide adequate supervision. In contrast, his teacher did not describe him as hyperactive or always on the go, and reported that he did not run or climb excessively. She stated that he was an odd child who stayed in the corner of the classroom engulfed ''in his own world'' for minutes until his impulsivity kicked in. She reported that he lost his temper frequently, which almost always ended with destruction of property or physical aggression toward others. She said she felt as if she could not get through to C. She also reported that he was not liked by his peers, and other children either were afraid of him, or teased him. He could not join peer groups and was reportedly shunned by peers because he always said unrelated things, or made bizarre comments.

Mother reported that C. enjoyed watching Disney movies from which he memorized lines and uttered them in unrelated places and out of context. He reportedly became fixated on topics (cars, names) and he ruminated on these for days. He especially became fixated on a girl's name (who left their neighborhood a year ago), and repeatedly asked questions and made comments about her. Mother and his teacher denied any stereotypic movements. C. also had begun to have crying and shouting spells. He would say things like ''my mother hit me,'' or ''my teacher beat me up,'' and mother reported that he often made things up.

After initial evaluation, C. was slowly tapered off of stimulants and atomoxetine. He was then switched to aripriprazole 2 mg, which was titrated up to 10 mg. Mother reported that his sleep schedule became erratic and that he only slept 3–4 hours. His shouting fits increased to the point that police came to their apartment four times in one week. His fits were reportedly triggered by child voices that he claimed that he heard. Mother said that he became especially sensitive to voices of other children on the street or babies crying in their apartment building. At this time, he also started to claim that he often saw a man he called Mr. V. creeping behind walls. Mother reported that he started hitting windows and

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walls in an attempt to catch and punish Mr. V. Mother said Mr. V. is a family friend with whom C. had a brief contact 2 years ago. He refused to be left alone in the room out of fear that Mr. V. would take him. Mother reported that they had to throw away or cover all the mirrors because he claimed he saw Mr. V. or other children in them.

As a result of the increase in C.'s symptoms, hospitalization was considered; however, he was maintained at home due to the lack of available hospital beds. A leave of absence from school was recommended, and C. started receiving special education at home. Valproate (VPA) was added to his aripiprazole, and the dose was titrated to a blood VPA level of 97. Risperidone was subsequently added to the regimen, and was titrated to 1 mg twice a day (bid). With the addition of valproate and risperidone, C.'s impulsivity decreased, his sleep cycle returned to normal, and the intensity of his fears decreased. He did not have any notable adverse effects other than a weight gain of 2.3 kg.

After a two-week period of partial improvement, C.'s perceptual disturbances recurred with increased severity despite continuation of the same medications. At one point, only delusions and hallucinations were present without mood symptoms. Aripiprazole and risperidone were discontinued, and he was switched to olanzapine, which was titrated to 15 mg daily. C. was continued on olanzapine for two months with reduction in his auditory hallucinations, but no changes in aggressive impulsivity. Notably C. did not become sedated on the combination of olanzapine and valproate; however, his symptoms started to increase again after two months, At that time, C. dropped out of treatment, as his mother wanted to seek treatment elsewhere.

C. and his mother returned after three months, and mother reported that his symptoms worsened after an initial period of improvement with valproate and quetiapine up to 600 mg daily. C.'s impulsivity and aggression resulted in legal difficulties when C. reportedly killed the family puppy by throwing him out of the window. C. was subsequently started on paliperidone, and the dose was titrated up to 6 mg while therapeutic doses of valproate were maintained. Decrease in impulsivity and complete dissolution of perceptual disturbance occurred on this regimen. There were no adverse effects on this combination of medications. In addition, C. was able to use public transportation without problems, hold reciprocal conversations for 5 minutes, and form 8–10 word sentences. C. was observed as more organized, and was able to draw meaningful pictures. He returned to school for special education. He continued to demonstrate minor impulsive aggressive behaviors (throwing small objects at others), which were managed by a full-time aide in class. At home, he reportedly was mostly calm and cooperative, with a reduction in frequency of tantrums and aggressive outbursts from every five minutes to twice a day.

Past Psychiatric History

C. had initially been evaluated at age 3 years, and a diagnosis of attention-deficit/hyperactivity disorder (ADHD), combined type was given. A second evaluation by a child psychiatrist resulted in a diagnosis of schizophrenia of childhood onset, with recommendation for risperidone. The family did not follow through on that recommendation.

C. was unable to cooperate with cognitive and academic assessments twice.

There is no reported history of abuse or neglect. There is no history of self-harm.

Developmental History

C. was the product of a complicated delivery at term, with breech presentation requiring vacuum extraction. There was reportedly no hypoxia and he did not need ICU care. Gross motor development was reportedly normal, but he had difficulty with fine motor skills. He began speaking at age 3 years with 2–3 word sentences. He was able to speak more clearly at age 5 years. A video from his fifth birthday showed him to be in good spirits, establishing good eye contact, spontaneously sharing, and using clear language appropriate to his age. His conversation was noted to be slightly perseverative, repeating the same girl's name.

Mother reported that C.'s verbal skills had deteriorated in the past year, but he was still able to form 5–6 word meaningful sentences.

Educational History

C. initially attended kindergarten. At age 6, after 2 months in first grade, he was switched to a special education program. After two months in the special education class, C. was recommended for in-home special education because of his impulsive aggression and risk of harming others. Despite his irregular school attendance, he was able to learn all his letters. He was able to do single-digit additions but not subtractions.

Social History

C. is the only child of a middle-class typical Turkish family. Mother and father are both teachers. He has a cousin his age with whom he played with when he was a toddler. He reportedly had some peer relationships in the past, but he recently lost all his friends and play dates due to his aggressive behavior toward other children.

Family History

Mother has had panic attacks and anxiety disorder. Maternal aunt is reported to have depressive episodes and episodes of mood elation, but has never received a formal diagnosis of bipolar disorder.

One paternal cousin was diagnosed with ADHD and learning disabilities.

There is no other known psychiatric history or any history of consanguinity, genetic or neurological illness in the family.

Medical History

C. had no serious medical problems, hospitalizations, or surgery. There is no history of epilepsy. C. had two normal EEGs at age 4 and 6, and a normal cranial MRI. Screening for metabolic and genetic disorders (including fragile X syndrome) ruled out such disorders. Complete blood count and chemistry screens were within normal limits.

Mental Status Examination

C. was an uncooperative child with an elongated face, wide forehead, big ears, and slightly protruded tongue whose behavior was difficult to control during the visit. He was evaluated while his mother was present. He wanted to draw a picture, threw the picture on the floor, and looked at his mother frightfully. When redirected by his mother, C. claimed that the interviewer had punched him in the face. He perseverated on a specific girl's name for a while, and repeatedly asked when he would eat his snack. C.'s drawing included erratic circles and lines, which he impatiently scribbled and

later claimed were a house and a dog. He kicked the table and threw a toy at his mother's face.

During the interview, C. had brief 3–5 minute periods of calmness, when he was able to ask proper questions, such as if needles are involved in today's visit. C.'s eye contact was fleeting, but he always looked when his name was called. His speech was baby-like and somewhat slurred. It was of note that he called his parents by their first names, which is very unusual in this culture. He repeatedly uttered song lyrics, sounding robotic.

No tics or abnormal movements were observed. He was hyperactive and restless. His affect was labile with sudden changes of mood. Thought content had some bizarre elements and was rigid and unusual. Thought process was disorganized; C. went on a different tangent when he tried to answer a direct question, or perseverated on unrelated words. Visual perceptual disturbances or internal preoccupation were suspected, evidenced by sudden attacks to the wall or suddenly acting on an impulse. C.'s cognition may have been mildly impaired; he knew his letters but could only write a few short words, became confused about the names of colors, and could not count past 20 or name the days of the week. His insight and judgment were both impaired.

Brief Formulation

In summary, C. is a 7 ½-year-old, right-handed, Turkish boy who meets diagnostic criteria for PDD-NOS and childhood onset schizophrenia, notable for longstanding problems with impulsive aggression and social relatedness. His course of illness is significant for its pervasive and unremitting quality with deterioration of emotional, social and cognitive functioning over time. He had early developmental signs of language deficit and hyperactivity from age 3, with notable perceptual disturbance at age 5. A major mood disorder was considered, given the period of decreased need for sleep and a possible underlying bipolar diathesis. C.'s cognition was impaired, which may have resulted from a cognitive decline associated with his psychosis.

C.'s response to paliperidone gives reason for cautious hope; however, C.'s course had been characterized by initial response to several different atypical antipsychotics followed by relapse, and thus it may be too early to evaluate the results of this trial. The combination of PDD symptoms, psychosis and unremitting impulsivity were clearly severely debilitating for the child and his family, and his treatment response to several different antipsychotics and combinations merit careful follow-up and monitoring.

Multi-Axial Diagnoses

Axis I:	PDD-NOS Childhood onset schizophrenia Rule out bipolar disorder
Axis II:	Rule out borderline intellectual functioning
Axis III:	None apparent
Axis IV:	Level of psychosocial stressors: severe; unable to attend to school
Axis V:	Current Global Assessment of Functioning score: 25

Discussion

This case illustrates the challenges of diagnosis in an early-onset neurodevelopmental disorder in which the symptom picture evolves over time. In retrospect the first diagnosis of ADHD did not take into account his cognitive, language, and social deficits, as his primary symptoms of most concern to his family and school were severe impulsivity and aggressive behavior. These, of course, are non-specific, pervasive symptoms that can occur in many early-onset neurodevelopmental disorders as well as disruptive behavior disorders. As these symptoms were associated with significant functional impairment, early treatment with medication was necessary. It is often the case that stimulants and nonstimulant medications are initial treatments for disruptive behavior symptoms in very young children that may evolve into psychotic or major mood disorders. That said, it became clear as C.'s clinical course evolved that ADHD treatments were inadequate for the more severely impairing social and cognitive deficits.

It is also not unusual for early-onset autism spectrum disorders such as PDD-NOS to evolve into a more clearly defined picture of psychotic illness as development proceeds, especially in the case of cognitive limitations. Although older literature suggested that autism was a distinctly different illness from early-onset schizophrenia, it may be difficult to differentiate the two, as there can be overlapping symptoms (Rutter 1972; Dosseter 2007). There is also emerging evidence that childhood onset schizophrenia and autism have clinical and biological links. In the two large studies that have examined this systematically, childhood onset schizophrenia is preceded by and comorbid with pervasive developmental disorder in 30%–50% of cases (Rapoport et al 2009). As autism spectrum disorders may present with social impairment, language deficits, impulsivity and aggressive behavior, it can be difficult to disentangle the presence of a new onset psychotic or major mood disorder. Disorganized thought and speech, cognitive impairments and aggressive behavior can be present in both autism spectrum disorders and early onset schizophrenia. DSM-IV-TR (American Psychiatric Association 2000) notes that although PDD and schizophrenia share disturbances in language, affect and social relatedness, PDD is usually recognized in early childhood. PDD is also characterized by absence of prominent delusions and hallucinations, with more perseverative or impulsive behavior or abnormalities in prosody. A diagnosis of schizophrenia is made only if prominent hallucinations or delusions have been present for at least a month (American Psychiatric Association 2000). Differential diagnosis is also more challenging in cognitively impaired children.

Another interesting and challenging aspect of C.'s clinical course is his apparent initial response to medications, including antipsychotics, followed by recurrence or relapse of symptoms. Of course it would be important to ascertain whether the family was able to adhere to the recommended treatments. At one point they were lost to follow-up when they sought another treatment setting. Although there would be no specific reason to suspect that non-adherence was an issue, it is a well-described phenomenon in both youth and adults that non-adherence can play a significant role in apparent relapse and recurrence. It is also possible that C.'s comorbid PDD and childhood onset schizophrenia may have rendered him more likely to be relatively treatment resistant to monotherapy with one antipsychotic. It is interesting that C. apparently showed at least some initial response to aripiprazole, risperidone, and olanzapine, but relapsed after some exposure at therapeutic doses. The addition of valproate may have been beneficial, but response is not specific for either childhood onset schizophrenia or pediatric onset bipolar disorder.

C. appeared, at least to date, to respond favorably to paliperidone. Unfortunately there is very little data on treatment of psychotic illness or severe aggressive behavior with paliperidone in children and adolescents. Paliperidone (9-hydroxyrisperidone) is the primary active metabolite of risperidone. It is marketed with a delayed release (ER) formulation in 3, 6 and 9 mg tablets and has an indication for treatment of schizophrenia in adults. A 16-week open label study of 18 children, ages 7–17 years, with severe behavior disorders previously treated with risperidone, evaluated the benefit of paliperidone in reduction of severe irritability. These patients had been treatment refractory to risperidone 1.5–2.0 mg for six months. In this open trial the youth were treated with paliperidone 3 mg daily; results indicated mean reduction in clinical global impressions (CGI)-severity score from 6.22 (0.65) to 4.50 (1.34) with difference of 1.72 (1.27) points ($p < 0.001$). Half the patients experienced marked improvement. Aggressive behavior, as measured by parent rated Overt Aggression Scale, decreased significantly from 2.7 (0.92) to 1.5 (0.60) ($p < 0.001$). Paliperidone was generally well tolerated; drowsiness led to discontinuation in one subject; mild dyskinetic movements were noted in one subject. There was no significant weight gain reported (Fernandez-Mayoralas et al 2012). In another study in children and adolescents, (Joshi et al 2013) studied 15 youth with bipolar spectrum disorders in an 8-week, prospective, open label trial of paliperidone; 11 (73%) were completers. At a total daily dose of 3 mg in 12 subjects and 6 mg in 3 subjects, paliperidone was associated with statistically significant reduction of manic symptoms on the Young Mania Rating Scale (18.7 ± 13.9, $p < 0.001$) from baseline to endpoint, and improvement of ADHD and psychotic symptoms. In this study, mean weight gain of 1.9 ± 2.5 kg was reported (Joshi et al 2013).

As an extended-release controlled oral delivery system, paliperidone may have some advantages over immediate-release formulations, as peaks and valleys in plasma concentrations may be minimized. This may reduce likelihood of adverse effects, and potentially facilitate adherence to treatment. Whether efficacy is demonstrated or adverse metabolic effects are more or less problematic than other antipsychotics awaits controlled investigation.

Acknowledgments

We would like to acknowledge and thank Resham Gellatly and Laura Ibanez-Gomez for their assistance in review and preparation of the manuscript.

Disclosures

Dr. Taskiran has no conflicts of interest or financial ties to disclose. Dr. Coffey has received research support from Eli Lilly Pharmaceutical, NIMH, NINDS, Tourette Syndrome Association, Otsuka, Shire, Bristol-Myers Squibb, Pfizer, and Boehringer Ingelheim.

References

American Psychiatric Association. *DSM-IV-TR*. 2000.

Dossetor D: ''All That Glitters Is Not Gold'': Misdiagnosis of psychosis in pervasive developmental disorders—a case series. Clin Child Psychol Psychiatry12:537–548, 2007.

Fernández-Mayoralas D: Treatment with paliperidone in children with behavior disorders previously treated with risperidone: An open-label trial. Clin Neuropharmacology 35:227–230, 2012.

Joshi G, Petty C, Wozniak J, Faraone SV, Spencer AE, Woodworth KY, Shelley-Abrahamson R, McKillop H, Furtak SL, Biederman J: A prospective open-label trial of paliperidone monotherapy for the treatment of bipolar spectrum disorders in children and adolescents. Psychopharmacology 2013, Feb.

Rapoport J, Chavez A, Greenstein D, Addington A, Gogtay N: Autism spectrum disorders and childhood onset schizophrenia: Clinical and biological contributions to a relationship revisited. J Am Acad Child Adolesc Psychiatry 48:10–18, 2009.

Rutter M: Childhood schizophrenia reconsidered. J Autism Child Schizophr 2:315–337, 1972.

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