JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 24, Number 6, 2014

Pp. 354–356
DOI: 10.1089/cap.2014.2462

Lurasidone Treatment in a Child with Autism Spectrum Disorder with Irritability and Aggression

Presenters: Hun Millard, MD, MA,[1] and Jennifer L. McLaren, MD[1]
Discussant: Barbara J. Coffey, MD, MS[2]

Chief Complaint and Presenting Problem

D. is a 13-year-old boy with intellectual disability and autism spectrum disorder (ASD), referred for evaluation of irritability and aggressive behavior.

History of Present Illness

D.'s mother initially became concerned about his development in his first year of life. She described D. as an irritable, colicky, and fussy baby with whom it was difficult to bond. He made little eye contact, preferred to play alone, had sensory sensitivities (e.g., to rough textured foods and clothing tags), and lacked a reciprocal social smile. At 18 months of age he had no language and was delayed in gross and fine motor skills. By 19 months of age, he had undergone a comprehensive early developmental evaluation which included audiology and ophthalmology assessment, chromosomal analysis and fragile X study, magnetic resonance imaging (MRI) scan, Achenbach Behavior Checklist, and child development specialty consultation. Genetic testing revealed normal Fragile X study, normal Neogen screen, and normal DNA analysis. MRI scan was normal. Results indicated a diagnosis of pervasive developmental disorder.

Subsequently, D. began to receive early intervention services including speech therapy, occupational therapy, and physical therapy. At 28.5 months, he was diagnosed with autism spectrum disorder by a developmental pediatrician because of his marked impairment in eye contact, lack of shared enjoyment, and poor social/emotional reciprocity. He enjoyed playing alone, and if left on his own he was reported to play for hours at a time, stacking blocks, aligning toys, and working with puzzles. D.'s language development remained delayed; he produced a variety of sounds, including humming and repetitive noises, but was unable to produce meaningful sounds or single words.

D. struggled throughout his early childhood with underlying irritability and temper tantrums. Mother felt that his challenging behaviors could be managed with behavioral interventions, and D. received behavioral supports from an applied behavior analysis based program.

D.'s mother described him as a fun-loving child who was active and enjoyed the Special Olympics. He was reported to have a strong interest in computers, and a fascination with Google images of movie covers, fires, and all things related to McDonald's and Burger King. Mother reported that D. often perseverated with one of these special interests, resulting in loss of temper and repeated aggressive behavior such as hitting himself when attempts were made to redirect him. Other aggressive behaviors included slamming the wall, throwing himself on the floor, hitting objects, and at times lashing out toward his mother, breaking her finger on one occasion. D.'s mother struggled with his insomnia, perseveration, anxiety, affective impulsivity, emotional dysregulation, self-abuse, and aggressive behaviors.

By age 12, D.'s irritability, temper tantrums, and aggression had escalated. At times he punched himself so hard he was giving himself black eyes. He was also struggling with significant hyperactivity and impulsivity and needed constant redirection, as reported by mother and observed on office visits.

Past Psychiatric History

There was no past psychiatric history other than what was described.

Developmental History

D.'s mother's pregnancy was complicated by gestational diabetes that was diet controlled. There was no nicotine, alcohol, or other toxin exposure during the pregnancy. D. was globally developmentally delayed in both motor and language milestones by 18 months of age.

Educational History

D. had received special education services starting at 3 years of age, and was in a classroom dedicated to education of children with ASD. He received speech therapy, occupational therapy, and physical therapy within the school program. D. also had a 1:1 paraprofessional for educational and behavioral support.

Social History

D.'s parents divorced when he was 4 years old. His father was often absent, as he had to work long hours. D. lived with his mother and older sister who was typically developing. There were no

[1]Geisel School of Medicine at Dartmouth, Department of Psychiatry, Lebanon, New Hampshire.
[2]Icahn School of Medicine at Mount Sinai, Department of Psychiatry, New York, New York.

recent changes in D.'s living situation. D. had no history of abuse and neglect. He had limited peer relationships.

Family History

D.'s mother had been diagnosed with depression, anxiety, and speech and language disorder. His maternal uncle had an unspecified cognitive disorder. His father had bipolar disorder, and his paternal grandparents both had hearing loss. There was no known family history of intellectual disability or ASD.

Medical History

D. had no history of serious medical problems, hospitalizations, or surgery. He had no history of seizure disorder or major childhood illnesses, and had received all appropriate vaccinations.

Medication History

D. was first started on medications at the age of 10 years. Initial treatment was with clonidine for insomnia and hyperactivity at 0.1 mg at bedtime (q.h.s.). Over a 1 year period, as behavioral problems worsened, clonidine was increased in 0.1 mg increments, to 0.4 mg q.h.s. with an additional 0.1 mg in the morning. Also, during this 1 year period, risperidone was initiated at 0.5 mg for perseverative behaviors and anxiety, but was discontinued because of adverse effects of increased appetite and weight gain. D. was subsequently started on citalopram 10 mg daily, which was initially noted to improve self-abusive and aggressive behaviors; after 3 months the dose was increased to 20 mg daily.

Clonidine was initially helpful with sleep, but insomnia continued to be a chronic issue. In addition to clonidine, 6 mg of extended-release melatonin was added for 1 month, and then hydroxyzine 25 mg q.h.s. for 2 months. At 10 years of age, D.'s primary outpatient provider referred him to a psychiatrist for further medication management.

Mental Status Examination

D. was a 13-year-old boy dressed casually in sweat pants and a T-shirt. No irritability, psychomotor agitation, or psychomotor retardation was noted. He exhibited occasional hand flapping. Speech was notable for echolalia, abnormal intonation, phrase-scripted speech, and no reciprocal conversation. No perseveration was noted, and D. expressed no homicidal or suicidal ideation. D. had no overt auditory/visual hallucinations or delusions. His mood was pleasant, with no irritability, but he showed constricted affect. While being interviewed, D. used few words, spoke in simple sentences when coached, and spontaneously used single words and nonverbal vocalizations to communicate. No aggression was noted, and D. responded well to redirection. His insight, judgment, attention, concentration, language, and fund of knowledge were poor.

Brief Formulation

In summary, D. is a 13-year-old right-handed boy who met criteria for ASD and attention-deficit/hyperactivity disorder (ADHD) requiring substantial supports for deficits in social communication, intellectual impairment, and self-injurious and aggressive behaviors.

From a biologic perspective, D. may have some genetic vulnerability to neurodevelopmental and psychiatric disorders, as his maternal family history is notable for an uncle with an unspecified cognitive disorder who was receiving Social Security Disability payments. Further, D.'s mother had been diagnosed with a speech and language disorder and affective illness, and D.'s father had received a diagnosis of bipolar disorder.

From a psychosocial perspective D. had a difficult start, with an often absent father and parents who eventually divorced when he was 4 years old. D. grew up in a family with financial and parenting challenges, which created stress and distraction for his mother. These stresses likely increased D's anxiety, and coincided with exacerbations in behavioral symptoms.

Medication Course

Upon initial psychiatric evaluation, hydroxyzine was discontinued and a plan for cross titration of clonidine and long-acting guanfacine was implemented, reducing clonidine to 0.2 mg q.h.s. and starting extended-release guanfacine 1 mg q.h.s. Quetiapine 50 mg as needed (p.r.n.) was prescribed for acute aggressive behaviors. One month later, D.'s mother reported that she had been giving D. quetiapine $\sim$4 times per week for acute agitation, but found that D.'s appetite increased. This created a new point of contention when more food was not immediately provided to him. Quetiapine was discontinued, and per mother's request, lorazepam, which had been used at a prior emergency department (ED) visit, was started at 0.5 mg p.r.n. for acute agitation.

After a 9-month period in which three clinic appointments were missed, D. returned at the age of 11 for follow-up. Citalopram was increased to 30 mg daily for impulsivity and rigidity, and extended-release guanfacine was increased to 2 mg q.h.s. for emotional reactivity and impulsivity. Four months later, D. was taken to the hospital for head banging and lashing out at others. D. was discharged from the ED on risperidone 0.5 mg q.h.s. One week after this ED visit, D. was re-evaluated by a psychiatrist. Since there was some behavioral improvement, risperidone was increased to 1 mg q.h.s., and 1 month after that, to 1 mg twice a day. In an effort to streamline medications, extended-release guanfacine was discontinued.

Three months later, D. was now 12 years old and had gained a significant amount of weight. He was reportedly gorging on food and at times eating out of the garbage can. The plan was to taper and discontinue risperidone over a 1-month period. Aripiprazole 5 mg per day was initiated. Aggressive eating behaviors declined on aripiprazole, but D. began to have daily episodes of vomiting; therefore, aripiprazole was discontinued after a 2-week trial and D. remained off antipsychotics for 1 month.

Over the next month, D. was noted to be more irritable, therefore aripiprazole was restarted at a lower dose of 2.5 mg per day, but daily vomiting returned. Aripiprazole was discontinued and extended-release guanfacine was restarted. D. was re-evaluated 1 month later with no measurable benefit from the extended-release guanfacine.

Therefore, lurasidone was initiated at 10 mg per day for irritability, perseveration, and aggression, and increased after 2 weeks to 20 mg per day. One month later, D.'s mother reported an improvement in irritability and aggressive behaviors. At a subsequent 4-month follow-up, D. was less irritable, aggressive, and hyperactive on 20 mg of lurasidone a day. As there were no significant adverse effects, the dose was increased to 30 mg per day, and trazodone was initiated for insomnia. Two months later, D. was noted to be significantly less irritable, aggressive, and impulsive on this combination, and he remains on lurasidone 30 mg daily, citalopram 30 mg daily, clonidine 0.2 mg q.h.s, and trazodone 75 mg q.h.s.

Discussion

This case illustrates the complexities and challenges of addressing a variety of symptoms in an early adolescent with ASD. The prevalence of ASD today is high, and some estimates demonstrate that 1 in 68 children are affected (Centers for Disease Control and Prevention 2014). There are currently no approved medications for treatment of the core symptoms of autism (social communication deficits). D.'s clinical course illustrates some common behavioral issues associated with ASD that present in clinical practice. The symptom domain of irritability refers to impulsive aggression, severe temper tantrums, or self-injurious behaviors (Doyle and McDougle 2012).

The use of antipsychotic medication for treatment of behavioral symptoms in children with ASD has become increasingly common, as this class of medication is considered to be the most efficacious for irritability in these children (Politte and McDougle 2014). A wide variety of antipsychotics have been studied, although risperidone and aripiprazole are currently the only Food and Drug Administration (FDA) approved medications for irritability associated with autism (Baribeau and Anagnostou 2014). Lurasidone is one of the newer antipsychotics and shows promise given its low adverse effect profile. It is presently FDA approved for the treatment of adult schizophrenia and bipolar depression. At the time of this report, there were no published studies of lurasidone in children with autism.

Lurasidone is an atypical antipsychotic with dopamine D2 and 5-hydroxytryptamine 2A (5HT2A) receptor antagonism. It also has 5HT7, 5HT1A, and noradrenaline α1c receptor binding affinity. Antipsychotics are thought to impact aggressive and impulsive behavior through regulation of dopamine and serotonin (Stahl 2013). Given the risk of long-term metabolic adverse effects of most atypical antipsychotics, lurasidone may serve as an alternative, as it has shown to have fewer effects on weight gain, hyperlipidemia, elevated blood sugar, and insulin resistance in adults. In addition to the favorable metabolic profile, lurasidone has been shown to have antidepressant effects in studies with adults. Mood benefits and decrease in depression and irritability are thought to be associated with 5HT7 and α2 receptor antagonism and partial 5HT1A agonist properties.

If first-line pharmacotherapy with risperidone and aripiprazole are ineffective or intolerable in adolescents with ASD then lurasidone may be a reasonable alternative, especially if the patient has a history of metabolic adverse effects. In addition to lurasidone's potential benefits for treatment of irritability in children with ASD there may also be a potential antidepressant effect, which may influence the overall symptom profile. As there are no existing published studies of efficacy of lurasidone in children with ASD, future research is needed.

Acknowledgments

We acknowledge and thank Zoey Shaw, Laura Ibanez Gomez, and Natasha Kostek for their assistance in review and preparation of the manuscript.

Disclosures

Drs. Millard and McLaren have no conflicts of interest or financial ties to disclose. Dr. Coffey has received research support from Boehringer Ingelheim, Bristol-Myers, Eli Lilly Pharmaceutical, National Institute of Mental Health (NIMH), National Institute of Neurological Disorders and Stroke (NINDS), Otsuka, Pfizer, Shire, and Tourette Syndrome Association.

References

Baribeau, DA, Anagnostou, E: An update on medication management of behavioral disorders in autism. Curr Psychiatry Rep 16:437–449, 2014.

Centers for Disease Control and Prevention (CDC), March 2014. Retrieved from http://www.cdc.gov/ncbddd/autism/facts.html.

Doyle, CA, McDougle, CJ: Pharmacotherapy to control behavioral symptoms in children with autism. Expert Opin Pharmacother 13: 1615–1629, 2012.

Politte LC, McDougle CJ: Atypical antipsychotics in the treatment of children and adolescents with pervasive developmental disorders. Psychopharmacology 231:1023–1036, 2014.

Stahl SM: Stahl's Essential Psychopharmacology, 4th ed. Cambridge: Cambridge University Press; 2013.

Address correspondence to:
Barbara J. Coffey, MD, MS
Icahn School of Medicine at Mount Sinai
One Gustave L. Levy Place, Box 1230
New York, NY 10029

E-mail: Barbara.coffey@mssm.edu