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Guanfacine Extended Release in Two Patients with Pervasive Developmental Disorders

Kelly Blankenship, D.O., Craig A. Erickson, M.D., Kimberly A. Stigler, M.D., David J. Posey, M.D., and Christopher J. McDougle, M.D.

To the Editor:

Pervasive developmental disorders (PDDs) are characterized by impairment in social interactions, deficits in communication, and repetitive behaviors/interests. Individuals with PDDs commonly exhibit other interfering symptoms, including inattention, hyperactivity, and impulsivity (American Psychiatric Association 2000). A study by Lecavalier (2006) with 487 nonclinically referred children and adolescents with PDDs (mean age 9.6 years) found that ~50% exhibited moderate to severe hyperactivity and/or inattention.

For typical children with attention-deficit/hyperactivity disorder (ADHD), methylphenidate (MPH) is the psychopharmacologic treatment of choice (Greenhill et al. 2002). However, the data for prescribing medication to children with PDDs and other developmental disabilities who exhibit inattention and hyperactivity are not as clear. Early studies concluded that children and adolescents with autistic disorder or intellectual disability responded poorly to stimulant medication (Aman 1982). However, more recently, a randomized, controlled, crossover trial of MPH in children with PDDs was performed by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network (RUPP 2005). They found that 35 of the 72 (49%) children were responders as judged by the Aberrant Behavior Checklist Hyperactivity subscale and the Clinical Global Impressions-Improvement (CGI-I) scale. Thirteen of the 72 (18%) individuals discontinued the study due to side effects, most commonly irritability. Based upon the modest efficacy and relatively poor tolerability of MPH, other agents used to treat inattention and hyperactivity in this population have been studied.

Guanfacine immediate release (IR) is FDA approved to treat hypertension in adolescents and adults. This short acting form of guanfacine has been used clinically (''off-label'') for the treatment of ADHD in typical developing children and for treating inattention and hyperactivity in PDDs (Posey and McDougle 2007). There are three published trials of guanfacine IR in children with PDDs. One was retrospective in nature, one prospective and open-label, and one was double blind and placebo controlled. These trials describe improvement in inattention and hyperactivity in some children (Posey et al. 2004; Scahill et al. 2006; Handen et al. 2008). Although guanfacine IR appears to be helpful for these symptoms, its use may be limited, at times, by a side effect profile that includes irritability and sedation. Concerns regarding hypotension should also be considered. Guanfacine IR is dosed two to four times daily due to a rapid peak plasma concentration and a precipitous decline (Sallee 2009). The half-life ranges from 10 to 30 hours with an average half-life of 17 hours (Merck 2010).

Recently, the FDA has approved guanfacine extended release (GXR) for the treatment of ADHD in children and adolescents. GXR can be prescribed alone or in combination with atomoxetine or stimulant medication to treat residual symptoms of inattention, hyperactivity, and impulsivity (Sallee 2009). The pharmacokinetics of GXR differ from those of guanfacine IR. GXR has a sustained release mechanism that helps to provide a steady plasma concentration over a longer period. When compared with guanfacine IR, GXR offers reduced peak-to-trough fluctuations that can improve tolerability and symptom control. The decreased frequency of dosing (once daily) may also increase compliance with medication. GXR has a half-life of 16 hours (Merck 2010).

Three randomized, controlled studies with GXR have been performed, all finding it effective for treating symptoms of ADHD (Biederman et al. 2008; Conner et al. 2009; Sallee et al. 2009). Biederman et al. (2008) performed an 8-week double-blind, placebo-controlled, fixed dose (2, 3, 4 mg) escalation study of GXR in 345 children aged 6–17 years with a diagnosis of ADHD. All groups of children receiving GXR showed improvement compared with the placebo group on the hyperactivity/impulsivity and inattentiveness subscales of the Attention-Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV), CGI-I, the Parent's Global Assessment and the Conners' Parent and Teacher Rating Scale-Revised: Short Form. Common side effects included headache, somnolence, fatigue, abdominal pain, and sedation. Conner et al. (2009) performed an 8-week, double-blind, placebo-controlled, flexible-dose (1–4 mg/day) study of GXR in 217 children aged 6–12 years with a primary diagnosis of ADHD along with oppositional symptoms. The group of children receiving GXR showed improvement compared with placebo as judged by the ADHD-RS-IV and the Conners' Parent Rating Scale-Revised: Long Form oppositional subscale. The most common side effects reported included somnolence, headache, sedation, abdominal pain, and fatigue. Sallee et al. (2009) performed a 9-week, double-blind, placebo-controlled, dose-ranging study with GXR (1–4 mg/day) in children aged 6–17 years with ADHD. Statistically significant reductions in ADHD-RS-IV scores were noted in all groups receiving GXR as compared with the placebo group. Common side effects included somnolence, headache, fatigue, sedation, dizziness, irritability, abdominal pain, and nausea. In

Christian Sarkine Autism Treatment Center, James Whitcomb Riley Hospital for Children, Indianapolis, Indiana.

these studies, GXR was considered well tolerated and efficacious compared with placebo.

In summary, individuals with PDDs commonly exhibit inattention, hyperactivity, and impulsivity that interfere with their quality of life. Given that guanfacine IR has shown some promise in the PDD population, it would seem that GXR could also reduce interfering symptoms in this population as well. Research to date suggests that in ADHD, GXR has a mild side effect profile, once daily dosing, and a more consistent plasma concentration as compared to guanfacine IR. In this report, we describe our clinical experience with GXR in 2 patients with PDD whom we treated.

Materials and Methods

The sample included two children, a 4-year-old with PDD not otherwise specified and a 9-year-old with autistic disorder. Diagnoses were made by board-certified child and adolescent psychiatrists using the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000). Written informed consent for treatment was obtained from the patients' legal guardians.

In both cases, GXR was initiated at 1 mg/day and increased, as tolerated, to treat the remaining inattention, hyperactivity, and impulsivity. Vital signs, including heart rate, blood pressure, height, and weight, were obtained at every follow-up visit. Global improvement, as measured by the CGI-I, was assigned by the prescribing physician at the time of last assessment. In this report, the CGI-I scale was focused on the target symptom domain of hyperactivity, inattention, and impulsivity. The CGI-I is rated from 1 to 7 (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse). Individuals were deemed responders to treatment if they were given a final rating of 1 or 2 (Leucht and Engel 2006).

Results

Case 1

A is a 4-year-old Caucasian girl with a developmental history that included abnormal eye contact and inappropriate social interactions. She was found to have a significant speech delay at 2 years of age. Her vocabulary has improved somewhat overtime. However, the quality of her communication remains quite impaired. Based on A's clinical presentation and history of inappropriate social interactions and speech delay, she was found to have PDD not otherwise specified based on DSM-IV-TR criteria.

In addition to exhibiting social and communication impairments, A also had a long history of severe inattention and hyperactivity. She was unable to listen, remain quiet, or follow directions. She had significant difficulty staying seated and fidgeted constantly. An atomoxetine trial was attempted before initiating GXR. This caused significant irritability and was discontinued after 2 months. Her maximum dose of atomoxetine was 10 mg BID (twice daily) (1 mg/kg). GXR was initiated at 1 mg/day for 3 weeks. Mild improvement was noticed in her ability to focus and in hyperactivity. However, these improvements would wane within 1–2 hours of ingesting the medication. Thus, GXR was increased to 2 mg/day. Per parent report, the target symptoms immediately improved. A was able to focus for longer periods and follow directions. She was able to stay seated for meals and movies.

Over her 8 weeks of treatment with GXR, she had significant improvement in inattention, hyperactivity, and impulsivity. Due to this notable decrease in these symptoms, she was judged to be "much improved," with a CGI-I score of 2. A tolerated this medication with minor difficulty. Her parents reported that she initially seemed sedated when the medication was increased to 2 mg/day. When the GXR was changed to 1 mg BID, the sedation improved. Before initiation of the medication, her blood pressure was 108/72 and her heart rate was 115. While taking the GXR 1 mg twice per day, her blood pressure was 102/72 and her heart rate was 94. A's body mass index (BMI) increased 0.08 in the 2 months she took the medication.

Case 2

B is a 9-year-old Caucasian boy with a developmental history including limited eye contact, deficits in social skills, and failure to develop age-appropriate friendships. B reportedly had a significant speech delay and he demonstrated repetitive behaviors such as rocking and spinning. He was initially found to have autistic disorder at the age of 2.5 years. At the time of presentation, his history and clinical examination remained consistent with the diagnosis of autistic disorder using DSM-IV-TR criteria.

In addition to exhibiting the above symptoms, B also showed significant irritability consisting of aggression and tantrums. He had been prescribed aripiprazole up to 20 mg/day 2 years ago and it provided partial relief of the irritability. B received concomitant treatment with this dose of aripiprazole during the entire trial of GXR. B had extreme difficulty listening and paying attention in the classroom and was unable to follow multiple-step directions. He was easily distracted and rarely able to finish his school work. He often forgot to remain seated in the classroom and he frequently disrupted the children near him. When attempts were made to redirect him, he would become angry and aggressive. An atomoxetine trial was attempted before initiating GXR. The atomoxetine caused significant irritability and was discontinued after a 1-month trial of up to 50 mg/day (1 mg/kg). GXR was initiated at 1 mg/day for 1 week and then increased to 2 mg/day. After the increase, significant improvement was noted in B's ability to recover faster from tantrums, which were also less frequent and intense. However, there was little improvement in inattention and hyperactivity. Thus, after 2 weeks the GXR was increased to 3 mg/day. After 3 weeks on this dose, B's mother reported a marked decrease in aggressive behavior, inattention, impulsivity, and hyperactivity. Due to this notable decrease in these symptoms, he was judged to be "much improved," with a CGI-I score of 2. After the increase to 3 mg/day, B's blood pressure was noted to decrease. Baseline vital signs revealed a blood pressure of 104/60, a heart rate of 98, and a BMI of 29.1. After the increase of GXR to 2 mg/day his blood pressure was 112/60 and heart rate was 86. After the increase of GXR to 3 mg/day, his blood pressure dropped to 98/52, his heart rate was 86, and his BMI increased to 29.3. He did not have symptoms consistent with hypotension. Due to the drop in blood pressure, he was evaluated by his primary care physician who approved the continued use of the medication. B has remained on the 3 mg dosage for the past 2 months. It continues to be effective for his inattention, hyperactivity, impulsivity, and aggression. His blood pressure remains similar to the above reading; however, he continues to remain asymptomatic.

Discussion

The study of GXR is very important and relevant to children with PDDs due to high rates of hyperactivity and inattention and decreased tolerability and modest efficacy of stimulants in this population.

This report illustrates our initial clinical experience with GXR in two patients with PDDs. Both patients were judged to be ''much improved'' on the CGI-I in inattention, hyperactivity, and impulsivity. In addition, in Case 2, there was also noted improvement in aggression.

The effectiveness of GXR in these 2 cases is not surprising given the reports of symptom improvement in the PDD population with guanfacine IR. In both of these cases, the patients were unable to tolerate atomoxetine due to irritability.

Overall, GXR was well tolerated. At the lower doses, no side effects were reported. However, at the higher doses, sedation and reduced blood pressure occurred. The complaint of sedation was not surprising given results from a prior study by Sallee et al. (2009) describing somnolence, sedation, and/or fatigue events in 49% of subjects. In this same study, 10% of the subjects exhibited hypotension/decreased blood pressure (Sallee et al. 2009). Many of the adverse reactions attributed to GXR appear to be dose-related (Sallee 2009).

Limitations

There are a number of factors that limit this report. Only two patients are described and the treatment was unblinded and uncontrolled. Further, Case 2 received aripiprazole throughout the trial of GXR. The diagnoses were not verified with standardized instruments. Other than the CGI-I, prospective rating scales were not used to collect baseline measures and then changes in target symptoms. Also, systematic adverse effect inventories were not collected.

Clinical Significance

This report provides preliminary data on the use of GXR targeting hyperactivity, inattention, and impulsivity in the PDD population. The results suggest that GXR may be an appropriate treatment for these symptoms in some patients. Future controlled studies are needed to further assess the efficacy and tolerability of GXR in patients with PDDs.

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Address correspondence to:
Christopher J. McDougle, M.D.
Department of Psychiatry
Indiana University School of Medicine
Institute of Psychiatric Research, PR 113
791 Union Drive
Indianapolis, IN 46202-4887

E-mail: cmcdougl@iupui.edu