Duloxetine Alleviates Stimulant Dysphoria, Helps With Enuresis, and Complements Cognitive Response in an Adolescent With Attention-Deficit/Hyperactivity Disorder

To the Editor. Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly encountered child and adolescent psychiatry disorders in clinical practice with a worldwide prevalence of 5%.[1] Stimulants are a first-line treatment modality in the ADHD pharmacotherapy guidelines.[2] Yet, 20% to 35% of subjects in clinical trials show inadequate response that could be attributed, in part, to dose-limiting side effects of medications or disorder severity or complexity.[3] Stimulant-related anxiety exacerbation is commonly cautioned in the pediatric population.[4]

Here, a case is reported of an adolescent with ADHD who failed an adequate trial of atomoxetine and showed a mediocre response to methylphenidate but experienced dysphoria that blunted the clinical response. Add-on duloxetine alleviated stimulant-induced anxiety, set off comorbid enuresis, and, strikingly, complemented the cognitive response. This response with duloxetine was achieved with high tolerability, which might provide new treatment options in such difficult-to-treat scenarios.

Case report. A 14-year-old Kuwaiti boy presented to a mental health center with his parents for evaluation of scholastic underachievement coupled with some mischievous behavior. He was the oldest of 6 siblings. He was delivered via full-term uncomplicated elective cesarean section and had developed normally. His parents recalled that as a toddler, he was fussy and colicky, was adventurous and curious exploring his surroundings, played with toys for only short periods of time, and was destructive and threw excessive tantrums. He had a history of episodic bronchial asthma that was treated with nebulized salbutamol as needed, but he no longer had asthma at the time of presentation.

During elementary school, the patient was described as overactive with frequent risk-taking behaviors such as crossing the street carelessly paying no attention to vehicles. As the patient got older, he often was noticed to be daydreaming. His mother always criticized him for being messy, forgetful, and a loser. His few friends were those who could withstand his moodiness. He was markedly below par in academics. Teachers always reprimanded him for teasing his peers, being noisy in the classroom, arguing too much, and, above all, being opinionated. Remedial teaching was not that helpful. He was held back this semester.

Family history was noted for a paternal uncle with major depressive disorder, who was maintained on fluoxetine. There was no history of smoking or illicit drug use, head trauma, epilepsy, toxic exposures, or tics. The ophthalmologic/otorhinolaryngologic evaluation was noncontributory. He had occasional enuresis, more often nocturnal, at a frequency of 3 to 4 times per month. The enuresis was thoroughly investigated in the urosurgical clinic for secondary causes, but nothing was found. He failed a trial of desmopressin acetate and another of oxybutinin. An adult psychiatrist in a private facility had diagnosed the patient with *DSM-5* ADHD–combined presentation with comorbid oppositional defiant disorder and prescribed atomoxetine titrated to 40 mg/d (weight = 70.5 lb [32 kg]) for about 2 months with no tangible response, as reported by the patient and parents and consistent with school records.

Following presentation to the mental health center, an extensive workup was pursued to rule out "counterfeit ADHD." Thyroid function tests were within normal limits as were iron studies. An electroencephalogram showed no abnormalities. The Vanderbilt Assessment Scales for ADHD,[5,6] both parent and teacher versions, were administered and confirmed the diagnosis of ADHD–combined presentation, severe with comorbid oppositional-defiant disorder. His IQ was was 85, as measured with the Wechsler Intelligence Scale for Children–Third Edition.[7] His Hamilton Anxiety Rating Scale (HARS)[8] score was 29. A Digit Symbol Substitution Test (DSST)[9] was conducted. Electrocardiogram results were within normal limits.

Immediate-release methylphenidate was titrated to 30 mg in 3 divided doses over 2 weeks. For convenience, he was shifted to long-acting methylphenidate 36 mg as a single-morning dose. The patient's response plateaued, rated as fair by his parents, but he still exhibited scholastic underachievement, albeit better behavioral facets. Methylphenidate was titrated to 54 mg with no ostensibly added benefits. Enuresis remained a problem. Moreover, the parents repeatedly reported that the patient experienced too much anxiety concomitant with the medications.

A trial augmenting methylphenidate with duloxetine was suggested and fully explained to the parents, who consented to its use as did the patient. Baseline liver function tests were obtained and were within normal limits. Duloxetine 30 mg was administered with meals to minimize anticipated nausea. Response was assessed over weeks 4, 8, 12, and 24 using parent and teacher reports; readministered Vanderbilt Assessment Scales for ADHD, HARS, and DSST; and number of dry nights. The outcome was impressive; his anxiety markedly diminished (HARS score reduced to 14), enuresis totally ceased, and, more strikingly, cognitive response was more enhanced. Duloxetine was highly tolerated. No drug-drug interactions with methylphenidate were noted.

The utility of duloxetine in ADHD might be ascribed to its boosting norepinephrine tone via serotonin-norepinephrine reuptake inhibitor mechanism of action—akin to similar efficacy of venlafaxine.[10] Niederhofer[11] reported some improvement across cognitive/behavioral domains using duloxetine monotherapy. Bilodeau et al[12] conducted a 6-week randomized placebo-controlled pilot study enrolling 30 adults with ADHD that was promising.

Mahmoudi-Gharaei et al[13] conducted a 6-week open-label study involving 17 adolescents with ADHD and reported improvement across all 4 subsets of the Conners' Parent Rating Scale–Revised with great tolerability. Recently, Strawn et al[14] reported a positive randomized controlled trial of duloxetine for treatment of generalized anxiety disorder in children and adolescents.

Efficacy of duloxetine in the treatment of stress urinary incontinence is associated with reuptake inhibition of serotonin and norepinephrine at the presynaptic neuron in Onuf's nucleus of the sacral spinal cord.[15] This association might explain our finding in this case report. All of these results converge to highlight a new treatment option for difficult-to-treat ADHD cases, especially with comorbid anxiety and enuresis.

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