Duloxetine May Improve Some Symptoms of Attention-Deficit/Hyperactivity Disorder

To the Editor: Dextroamphetamine[1] and methylphenidate[2] are first-line agents for the treatment of attention-deficit/hyperactivity disorder (ADHD). Despite the impressive track record of stimulants in the treatment of ADHD, they fail in 25% of patients due to lack of efficacy or the emergence of unwanted side effects.[3]

With respect to nonstimulants in the treatment of ADHD, the α_2-receptor agonist clonidine has been used for more than 20 years,[4,5] showing medium effect. The findings from controlled studies, however, have been somewhat inconsistent, showing benefit[6] and negative results.[7] The norepinephrine reuptake inhibitor desipramine has also shown some benefit.[7] The novel antidepressant bupropion was found to be superior to placebo.[8] Niederhofer[9] demonstrated that drugs affecting the serotonin system may also improve some symptoms associated with ADHD. Atomoxetine is a selective norepinephrine reuptake inhibitor and a unique ADD/ADHD medication, as it affects only norepinephrine, rather than dopamine. Norepinephrine and dopamine are structurally very similar, differing only in the presence of a hydroxyl group. As a result, atomoxetine has a lower abuse potential than psychostimulants.[10]

We found no study investigating the efficacy of duloxetine, a serotonin and norepinephrine reuptake inhibitor, in treating patients suffering from ADHD. For that reason, this observation was conducted to examine the effects of duloxetine on a variety of target behaviors in patients with ADHD.

Method. After screening procedures and a 7-day washout period were completed, informed consent was obtained, and comorbidities including hyperthyroidism, anxiety disorder, bipolar disorder, psychosis, electroencephalographic abnormalities, and suicidality were excluded, 2 male patients (16 and 19 years old) diagnosed with ADHD, inattentive type, received duloxetine (30 mg/d) for 4 weeks and placebo for 4 weeks. One of the patients received duloxetine before placebo, and the other received placebo before duloxetine. The patients had suffered from ADHD for at least 12 years. Prior to this medication, both subjects had received methylphenidate 30 mg daily for 6 years, which improved symptomatology, but led to insomnia and weight loss. The study was conducted from March 2008 to May 2008.

Patients were recruited from our clinic. Before study entry, the patients were seen for a detailed clinical evaluation by an interdisciplinary team consisting of a psychiatrist and a psychologist. The patients (Wechsler Intelligence Scale for Children-Revised IQs of 98 and 112) were free of all psychotropic medication for 1 week and free of any medical problem. They did not suffer from tic symptoms (Yale Global Tic Severity Scale[11] total tic score < 22) or obsessive-compulsive symptoms (Children's Yale-Brown Obsessive Compulsive Scale[12] total score < 15). An interview and Youth Self Report[13] were conducted to exclude anxiety disorder, depression, and psychosis. The screening included routine laboratory tests, electrocardiogram, measurement of pulse and blood pressure, height and weight measurement, medical history, and a physical examination.

The diagnosis of ADHD was made on the basis of this clinical interview and the ADHD Rating Scale-IV,[14] an 18-item measure (scores from 0 = never to 3 = very frequent) of inattention and hyperactive/impulsive symptoms derived from *DSM-IV*, which yields 3 scores: an inattention score and a hyperactive/impulsive score (range, 0–27 for each score) and a total score (range, 0–54). The means of the 3 scores were calculated.

Results. During duloxetine treatment, improvement was observed in the ADHD Rating Scale-IV inattention score (mean decrease from 14.3 to 9.2), hyperactive/impulsive score (mean decrease from 13.5 to 7.4), and total score (mean decrease from 27.8 to 16.6). Placebo showed mean scores similar to those of the before-treatment period: inattention score, 12.9; hyperactive/impulsive score, 13.6; and total score, 26.5. In the active-treatment period, there was a reduction of 2 points on the Clinical Global Impressions (CGI)-Severity of Illness scale[15] for ADHD symptoms, rated by a clinician who was blinded to whether the patients were receiving placebo or duloxetine. Placebo showed no CGI changes.

No serious side effects were observed by means of the Systematic Assessment for Treatment Emergent Events (SAFTEE).[11] There were also no alterations in laboratory test results, and the patients showed no clinically meaningful change in cardiac conduction. They complained of mild sedation, which soon subsided. There were no changes in weight from baseline to endpoint. To evaluate cardiovascular effects, we compared blood pressure changes at each visit and could not detect a change.

To the author's knowledge, this is the first observation of duloxetine in adolescents with ADHD. The observed improvement is lower than the 50%–60% improvement reported in stimulant trials,[12] but is similar to the level of improvement observed in studies of other nonstimulants, such as desipramine[16] or venlafaxine,[17] as add-on medications. This might be due to the fact that duloxetine acts only via the noradrenergic mechanism. This finding also raises questions about the utility of combining duloxetine with a stimulant. In patients with ADHD, this combination might permit lower doses of the stimulant. Furthermore, duloxetine could provide protection against tics. Questions about these effects can be answered only with further placebo-controlled, randomized studies of larger samples that focus on the safety and efficacy of monotherapy with duloxetine in this population.

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Helmut Niederhofer, MD, PhD
helmutniederhofer@yahoo.de

Author affiliations: Department of Child and Adolescent Psychiatry, Regional Hospital Bozen, Bolzano, Italy.
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