Atomoxetine Used Adjunctively With Selective Serotonin Reuptake Inhibitors to Treat Depression

Sir: The recent article by Manning[1] offers an excellent review of newer antidepressants available for family physicians treating patients with depressive disorders. Jain[2] points out, in a thorough article, that newer dual-action antidepressants mediating serotonin and norepinephrine have increased in scientific and clinical interest and may reduce the symptoms of depression more effectively than the selective serotonin reuptake inhibitors (SSRIs). Nelson et al.[3] also echo that a combination of serotonergic and noradrenergic agents is more likely to result in remission than either agent alone.

Three cases are presented in which patients diagnosed with depressive disorders responding to treatment with SSRIs achieved remission with the addition of atomoxetine, a norepinephrine reuptake inhibitor. All of the patients presented for treatment in 2003. The patients' areas of nonresponse were ongoing fatigue, low energy, and poor concentration. These patients were unable to tolerate dual-action antidepressants currently available on the market or had experienced side effects that were intolerable. Atomoxetine is approved for the treatment of attention-deficit/hyperactivity disorder,[4] and its use in depression is outside the scope of this U.S. Food and Drug Administration indication. A recent PubMed search on atomoxetine in the treatment of depression using the keywords *atomoxetine, depression,* and *treatment,* with no limitations on language or date of publication, revealed no reports.

Case 1. Ms. A is a 24-year-old woman diagnosed with major depressive disorder, recurrent, moderate (DSM-IV-TR[5] criteria). The current depressive episode was her second; she had experienced her first depressive episode at 21 years of age while in college and was treated with sertraline 150 mg/day for 1 year, achieving full remission. She was taking no medication at the time of consultation and was in excellent physical health. Results of a laboratory examination including a complete blood count and thyroid-stimulating hormone, hepatic, metabolic panel, and serum human chorionic gonadotropin measures were unremarkable. The patient was also diagnosed with generalized anxiety disorder. Her Hamilton Rating Scale for Depression (HAM-D)[6] score was 18.

Treatment options were discussed, and the patient agreed to a trial of venlafaxine extended release (XR) started at 37.5 mg/day. Within 48 hours, Ms. A developed a generalized rash and discontinued the medication. After the rash cleared, a trial of sertraline 50 mg/day was initiated without adverse effect. The patient's sertraline dose was increased to 150 mg/day over the course of 4 weeks with some improvement; however, she continued to experience low energy and decreased concentration that contributed to ongoing occupational problems. The sertraline dose was then increased to 200 mg/day with no changes after 2 weeks. Ms. A's HAM-D score decreased to 13, but it was felt that there was room for improvement in the areas of decreased energy and decreased concentration. Treatment options were discussed, including adding bupropion; however, the patient had been unable to tolerate bupropion taken during a smoking cessation class.

She agreed to a trial of atomoxetine started at 18 mg 2 times per day. No side effects were noted, and within 2 weeks Ms. A experienced improved energy and concentration. The patient's atomoxetine dosage was increased to 25 mg b.i.d. in an effort to return her energy to baseline, which helped her enough to get back into an exercise regimen. After 1 month on atomoxetine treatment, the patient had a HAM-D score of 4. She is doing well at work with full remission of depressive symptoms and remains in remission at 8 months.

Case 2. Ms. B, a 34-year-old woman, had diagnoses of dysthymic disorder and an eating disorder not otherwise specified per DSM-IV-TR[5] criteria. She was in good health although mildly overweight, by 15 lb (7 kg) in her estimation, and she took no medications. Results of her laboratory examination were unremarkable, and she agreed to a trial of fluoxetine 20 mg/day. Fluoxetine treatment was well tolerated, with an improvement in mood and less impulsivity at 3 weeks. Ms. B felt an ongoing sense of fatigue and an inability to sustain concentration. Her fluoxetine dose was increased to 40 mg/day with little improvement after 1 month. Treatment options were discussed; because of her eating disorder, bupropion was excluded, and the patient was concerned about possible weight gain with mirtazapine.

The patient agreed to the addition of atomoxetine started at 10 mg b.i.d. Ms. B experienced dry mouth but was able to tolerate an increase to 25 mg 2 times per day to target residual symptoms, achieving resolution within 2 weeks of the increase in dose. She is doing well at 5 months; she is working hard in interpersonal therapy and is compliant with her medication.

Case 3. Mr. C is a 36-year-old man diagnosed with major depressive disorder, recurrent, and alcohol abuse in remission. By his wife's account, since his initial depressive episode in his early 20s, he had not experienced a return to his baseline mood. He was in good medical condition but had experienced considerable occupational impairment due to his most recent depressive episode. In the past, he had taken paroxetine but had gained about 15 lb (7 kg) over the course of a year while taking that medication. He had also taken venlafaxine XR at the time of his second depressive episode 3 years previous to consultation but was unsure how long he had taken it or if it worked because at the time he was abusing alcohol. An attempt to obtain old treatment records was successful, and the patient had taken venlafaxine XR 150 mg/day with no sustained improvement. The patient's HAM-D score at the time of consultation was 19, and complaints of low energy, poor concentration, and lack of motivation were especially prominent. Mr. C agreed to a trial of escitalopram started at 10 mg/day with no adverse effects noted. At 2 weeks, the patient increased the medication dose on his own and experienced an improved mood but little else. He agreed to a trial of bupropion extended release (XL) 150 mg as part of an augmentation strategy but stopped taking it after 5 days due to excessive agitation, insomnia, and irritability.

After the patient received escitalopram 20 mg/day for 6 weeks, treatment options were discussed and the patient agreed to a trial of atomoxetine started at 18 mg twice per day, which was well tolerated. At 2 weeks, he began to notice some improvement in concentration; his dose was increased to 25 mg b.i.d. with sustained improvement in energy, concentration, and motivation. After 1 month of

treatment with atomoxetine 25 mg b.i.d. and escitalopram 20 mg/day, the patient's HAM-D score was 5 and he was back to work full time. He has remained in remission over the past 6 months.

In the cases described above, the patients were either unable to tolerate (due to side effects, cases 1 and 3) or unable to take (due to a contraindication, case 2) existing newer dual-action antidepressants that modulate norepinephrine reuptake. Atomoxetine, which was viewed as an antidepressant in 1985,[7] was added to SSRI treatment in these 3 patients, thus creating a dual-action regimen. Patients were able to achieve remission of their depressive conditions with treatment especially targeting their residual symptoms of fatigue, low energy, and decreased concentration felt to be due to dysregulation of the noradrenergic system along with attention, memory, arousal, and sleep.[8]

Caution is advised when interpreting case reports; however, the adjunctive use of atomoxetine with existing SSRI treatment may be of benefit especially to clinicians whose patients are unable to take existing newer dual-action medications. Further studies that evaluate atomoxetine in the treatment of depressive disorders may be warranted to help patients achieve remission.

Dr. Berigan has participated in visiting speakers bureaus for Wyeth and GlaxoSmithKline.

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