CASE REPORT

Suprathreshold Duloxetine for Treatment-Resistant Depression, Anorexia Nervosa Binge-Purging type, and Obsessive-Compulsive Disorder: A Case Report

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ABSTRACT

Duloxetine, a serotonin norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of depression, is used for off-label purposes such as treatment-resistant obsessive compulsive disorder, bulimia, and binge eating disorder. Although establishing a dose-response relationship for antidepressants in the treatment of depression is difficult, it is possible that for certain patterns of comorbidity, suprathreshold doses may be important to achieve remission. There is currently a paucity of literature regarding the use of suprathreshold doses of duloxetine in treatment refractory cases. This case report describes a clinical situation in which suprathreshold duloxetine was used to treat a patient with severe depression as well as co-morbid anorexia nervosa binge-purging type and obsessive compulsive disorder. One year after the initial increase to 180mg, the patient's mood remains improved. Our clinical account appears to be only the second case report describing the efficacy of high dose 180mg duloxetine in the management of symptoms refractory to treatment at standard doses.

INTRODUCTION

Dual reuptake inhibitors have been shown in a number of studies to have small but significantly greater rates of response and remission compared to selective serotonin reuptake inhibitors for the treatment of major depression.[1–6] Duloxetine, a serotonin norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of depression, generalized anxiety disorder, and certain forms of pain. It has also been used for off-label purposes such treatment-resistant obsessive compulsive disorder (OCD),[7,8] bulimia,[9] and binge eating disorder.[10]

According to the Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder,[11] SNRIs such as venlafaxine are recommended in cases where there is little or no response to traditional monotherapy treatments (e.g., selective serotonin reuptake inhibitors (SSRIs) or clomipramine).

Although establishing a dose-response relationship for antidepressants in the treatment of depression is difficult, it is clinically relevant to seek a more rapid response in patients with severe depression through higher doses of antidepressants. While empirical evidence is lacking, higher doses may also be important to achieve remission. We describe a case in which duloxetine effectively treated a patient with severe depression and comorbid anorexia nervosa, binge-purging type, as well as OCD. Our clinical account appears to be only the second case report[12] describing the efficacy of high dose 180mg duloxetine in the management of treatment refractory symptoms.

CASE REPORT

Ms. A., an 18-year-old single woman, was referred in the middle of her senior year of high school by her therapist for a medication evaluation regarding symptoms of depression, disordered eating behaviors, and anxiety. The patient had a history of depressed mood beginning in childhood but increasing since the 7th grade when she started to self-harm by cutting. She described not fitting in at school or at home and experienced a decrease in appetite. Subsequently she noticed enjoying the feeling of losing weight. Restriction was accompanied by purging (maximum of 3–4 times/day). By the winter of her junior year she lost 20 pounds, reaching a body mass index (BMI) of 18.3kg/m^2 (110 pounds at 5 feet 5 inches). She did not binge or use laxatives but excessively exercised. Her weight continued to drop despite beginning individual therapy and seeing a nutritionist in the spring. Beginning her senior year at 105 pounds (BMI: 17.5kg/m^2), she was admitted to the hospital for bradycardia (heart rate in the low 40s). She regained weight to 120 pounds but experienced a worsened depression, for which she was offered an antidepressant. Her parents refused.

Upon presentation in our clinic, Ms. A. met the criteria for major depression. She noted passive suicidal ideation with no current plan or intent. She denied current cutting but did admit to harming herself by hitting her ribs, hips, and knees with weights. She denied overt paranoia, visual or auditory hallucinations, or ideas of reference. She denied drug abuse and stated she drank alcohol infrequently. Her current weight was 54.7kg or 120.5 pounds (BMI: 20.1kg/m^2).

Ms. A. also reported significant OCD symptoms. Many of her rituals involved food, though the patient stated that these predated her eating disorder. For example, she recalled that even as a child she had to chew her food an equal number of times on each side of her mouth. She repeated phrases she heard over and over in her head and believed that choices she made during her morning routine—such as on which side of the sink she left her tube of toothpaste—determined the remaining course of her day. Family psychiatric history was significant for depressive loading on her father's side. In addition, one paternal first cousin had anorexia nervosa, another OCD, and a third schizophrenia. Her maternal grandfather was an alcoholic.

A trial of a selective serotonin reuptake inhibitor (SSRI) was recommended with citalopram chosen. Because of the family's reluctance concerning medications, the initial dose was 5mg. At follow-up two and one-half weeks later, the Ms. A. was tolerating 10mg of citalopram without side effects but felt more depressed and had lost five pounds. Citalopram was increased to 15mg with the plan to increase to 20mg. Her weight continued to drop despite follow up and the following month, at 99 pounds (BMI: 16.5kg/m^2), she was admitted for her second inpatient hospitalization for medical instability. Citalopram was increased to 30mg. Upon reaching medical stability after one week, she was transferred to an eating disorder residential facility for her anorexia, OCD, and comorbid depression—which included the suicidal plan to crash her car into a tree. During her four-month stay, citalopram was increased to 40mg before being discontinued due to lack of efficacy. Duloxetine 30mg was started and gradually increased to 80mg, at which point the patient reported a response. Low-dose aripiprazole was initiated and then discontinued due to excessive sedation, and was replaced with 0.5mg of risperidone as needed in the evening. The patient initially did well on this combination but after experiencing a worsening of her depression and suicidal ideation, duloxetine was increased to 120mg. This was associated with sustained improvement. Discharge medications were duloxetine 120mg per day and risperidone 0.5mg as needed at bedtime. Her discharge weight was 58.3kg (122.4 pounds; BMI: 20.4 kg/m^2).

The patient returned to clinic about one and one-half months later. Her mood was markedly improved and she denied suicidality. Her discharge weight had been maintained and she looked forward to starting college within the next month. Medications were continued at their current doses with the plan to begin individual therapy and an eating disorder support group at college.

After having attended college for one month, the patient contacted the clinic. She initially had adjusted

to school, started individual and group psychotherapy, and made friends but began to feel her depression return along with urges to cut herself. She reported being increasingly isolated and restricting her eating and also reported that she had begun purging. Risperidone was increased from 0.5mg to 1.5mg at bedtime and she was advised to raise her dosage of duloxetine from two capsules (each 60mg) to three capsules. The increase directly to 180mg was made because the delayed-release capsules could not be broken. She reported feeling improved after two days but asked to lower her risperidone back to 0.5mg due to excessive fatigue. After one week of stability at 180mg, she was prescribed 20mg capsules of duloxetine to prepare for a slow taper to her original dosage by increments of 20mg. The patient was able to tolerate 160mg. Though she noticed an increase in depressive thoughts and self-harm impulses, she felt able to control them. After one week, the dosage was decreased to 140mg whereupon she reported a marked worsening of depressive symptoms, eating preoccupations, and obsessional suicidal thoughts. Duloxetine was increased back to 160mg but the continued depressive and suicidal ideation led to the return of the 180mg dosage. Two further attempts to taper by 20mg were associated with a worsening of symptoms. The patient tolerated 180mg without significant side effects, and the decision was made to have her remain on 180mg despite this being above the normal recommended range.

One year after the initial increase to 180mg, the patient's mood remains improved. She is doing well in school, denies depression or suicidal ideation, and has stopped engaging in restrictive eating or purging. She notes that occasionally she gets distracted by a compulsion, such as to count when walking, but is able to resist. She continues her weekly psychotherapy and weekly eating disorder support group.

DISCUSSION

The literature regarding the use of suprathreshold doses of duloxetine is limited. Interestingly, our findings are similar to the one case report identified using 180mg.[11] In that report, a patient with severe OCD symptoms achieved significant improvement exclusively at that dose. The authors suggest that "monotherapy with high-dosage duloxetine (180mg/day) might provide another treatment option in treatment-resistant OCD, especially when the obsessive-compulsive symptoms are severe and lead to significant functional disability."[11] Our present case report of a patient with severe depression, anorexia, and OCD adds to this literature and further suggests that high-dose duloxetine be considered for patients whose symptoms tend to recur despite being on the maximal recommended dose.

We suggest that high-dose duloxetine may have been the key ingredient in this patient's recovery despite findings that 120mg/day, while effective, confer no additional benefits above 60mg.[13] However, such studies excluded patients with OCD. It is possible that for certain patterns of comorbidity, suprathreshold doses are necessary to achieve recovery. Though the safety of duloxetine above 120mg/day has not been adequately evaluated,[14] research indicates that 180mg/day duloxetine is safe for patient cardiac health.[15] Conversely, we cannot rule out that other factors might explain the patient's symptomatic improvement.

We hope that case studies such as this will stimulate further investigations into the potential efficacy of high-dose duloxetine for patients who fail to respond to recommended doses. Though the patient in this case study did not receive genetic typing, duloxetine is a substrate of CYP 2D6 and 1A2; the CYP 2D6 enzyme is associated with genetic polymorphism.[15] Hence further studies may examine the influence of pharmacogenetic factors, including the possibility that patients who fail to respond to recommended doses of duloxetine are ultra rapid metabolizers.

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