

Moving beyond first-line treatment options for OCD

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Abstract

OCD is characterized by obsessions and compulsions that cause distress, are time-consuming, and interfere with a patient's social, occupational, or other areas of functioning. SSRIs are first-line pharmacologic treatment options and produce response rates of up to 60% in patients with OCD. Several potential strategies have been evaluated for enhancing patient response, including high-dose SSRI therapy, antipsychotic augmentation, and memantine augmentation. Three patient cases are used to explore treatment guidelines, evaluate existing literature, and provide pharmacotherapy recommendations for the management of patients with OCD when first-line therapy fails.

Keywords: obsessive-compulsive disorder, selective serotonin reuptake inhibitors, antipsychotics, memantine

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Introduction

According to the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition*, criteria for a diagnosis of OCD include the presence of obsessions, compulsions, or both features.^{1,2} An obsession is an unwelcome and reoccurring thought, image, or impulse, whereas a compulsion is a repetitive act or behavior that an individual feels compelled to perform.¹ Compulsive behaviors are performed to reduce the anxiety caused by obsessions or to prevent a feared outcome; however, compulsions may not be related to the corresponding obsession in a meaningful way or are a disproportionate response to the obsession (Table 1).^{2,3} Obsessive-compulsive symptoms cause distress, are

time-consuming, and interfere with a patient's social, occupational, or other areas of functioning.² Patients with OCD generally recognize the symptoms as excessive or unwanted. While less common than disorders such as generalized anxiety disorder and posttraumatic stress disorder, the lifetime prevalence of OCD affects approximately 2.3% of adults in the United States.⁴ Roughly 1.2% of adults in the United States had a diagnosis of OCD in the past year, with higher rates in women than men.^{1,2} The prevalence of OCD in the pediatric population is approximately 1% to 2%, with higher rates in males.⁵

The etiology of OCD is not fully elucidated. Hyperactivity in the cortico-striato-thalamo-cortical pathways is present and decreases with successful treatment.⁶ Genetics appear to play an important role, with first-degree relatives of patients with OCD appearing to have a higher risk of developing the disorder than those without familial connections. Serotonergic neurotransmission may also contribute to the pathogenesis of OCD. Data for specific genetic variations affecting the serotonin system, such as serotonin transporter and serotonin receptor genes, are mixed. Studies evaluating serotonin transporter or serotonin-2A receptor binding have demonstrated both increased and decreased activity in patients with OCD.⁷

OCD follows a chronic, waxing and waning course.⁸ Symptom onset is gradual for most patients and generally



TABLE 1: Common obsessions and compulsions in adults^{3,13}

Obsessions

- Fear of contamination
- Concerns of harm
- Aggressive thoughts
- Need for symmetry
- Pathological doubt
- Somatic worries
- Religious preoccupation

Compulsions

- Washing
- Checking
- Counting
- Repeating
- Ordering
- Hoarding
- Need to ask or confess

occurs before the age of 25.^{2,3} The diagnosis of OCD may be delayed by as long as 10 years or more, preventing the start of treatment, because of clinician unfamiliarity with its variable presentation or by patient effort to conceal the disorder.³ The majority of patients with OCD have comorbid psychiatric disorders, such as MDD, bipolar disorder, and other anxiety disorders.⁹ Up to 30% of patients with OCD experience tic disorders.^{2,3} Approximately 25% of patients with OCD attempt suicide.⁹ Obsessions and compulsions are both generally present in pediatric patients; however, compulsions are noticeable and more easily identified.^{2,5}

When treating patients with OCD, goals of therapy include reducing symptom frequency, reducing symptom severity, and achieving remission.^{10,11} Beyond remission, the ultimate goal is to help patients achieve wellness. Wellness encompasses broad, interconnecting areas of life, such as physical (eg, improving physical health), social (eg, meeting people with similar interests), and occupational (eg, achieving balance between work and leisure) well-being.¹¹ Patients may need assistance with developing coping strategies.¹² Managing medication adverse effects, particularly when high doses are used, is essential for patient adherence.^{10,12}

Monitoring treatment efficacy is accomplished through the use of standardized rating scales.¹³ The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) is the gold standard, clinician-rated instrument for measuring the severity of OCD symptoms. Obsessions and compulsions are rated in several areas, ranging from the time spent on obsessive thoughts to the level of control a patient has over compulsive behaviors. The Y-BOCS consists of 10 total items, with 5 items for obsessions and 5 items for

Take Home Points:

1. SSRIs produce response rates of up to 60% when used for OCD. Guidelines recommend a trial of 12 or more weeks. For patients tolerating a maximum dose for the first 8 weeks without a satisfactory response, high-dose SSRI treatment can be considered.
2. Antipsychotic medications, such as aripiprazole and risperidone, possess antiobsessional properties and can be used adjunctively for patients who do not fully respond to SSRIs. Recommended dosing is typically lower than doses used for the treatment of schizophrenia.
3. Memantine has been investigated as a potential antidepressant augmenting strategy for patients with OCD. Current evidence does not support its routine use, and further study is needed before its place in therapy can be fully elucidated.

compulsions. Individual item scores range from 0 (none) to 4 (extreme) for a total possible score of 40. Individuals without OCD are expected to score 8 or less on the Y-BOCS.¹⁴⁻¹⁶ This rating scale assesses changes in symptoms over time. Guidelines¹⁷ generally define response as a 25% to 35% or greater decrease in Y-BOCS score from baseline. Initial improvement in OCD symptoms with pharmacotherapy may not be evident until at least 4 to 6 weeks of treatment.¹² The Clinical Global Impressions scale, often used in conjunction with other psychiatric rating scales, is a 3-item scale that measures illness severity and can be used to evaluate treatment response over time.¹⁶

Treatment guidelines¹² broadly support pharmacotherapy and CBT as first-line treatment options for OCD. SSRIs are first-line pharmacotherapeutic treatment options. Studies demonstrate response rates of up to 60% with SSRI treatment.^{6,9} A trial of 12 weeks or more, with an adequate dose, is needed to determine response to treatment.^{8,13} Antidepressant dosing is provided in Table 2. Doses can be titrated in weekly intervals in the first month when initiating pharmacotherapy.¹² If there is no response to treatment, consider a second SSRI before switching to a second-line treatment option, such as clomipramine, venlafaxine extended-release, or mirtazapine.⁹ CBT with behavioral techniques such as exposure therapy and response prevention is often combined with pharmacotherapy, and the combination has been shown to be more effective than medications alone.⁹ With exposure and response prevention, patients gradually confront feared situations and use coping skills to avoid performing compulsions, gradually lessening the patient's anxiety.¹² Antidepressant augmentation with antipsychotic medications is recommended by treatment guidelines.^{8,9,12,13} Transcranial magnetic stimula-

TABLE 2: Antidepressant dosing for adult patients with OCD^{12,28}

Antidepressant	Usual Dose (mg/d)	FDA Approved Maximum Dose (mg/d)	APA Guideline Occasional Maximum (mg/d) ^a
FDA approved			
Clomipramine	100-250	250	TDM ^b
Fluoxetine	40-60	80	120
Fluvoxamine	200	300	450
Paroxetine	40-60	60	100
Sertraline	200	200	400
Not FDA approved			
Citalopram	20-40	40	120 ^c
Escitalopram	20	20	60

APA = American Psychiatric Association; TDM = therapeutic drug monitoring.

^aOccasional maximum doses are not FDA-approved.

^bCombined clomipramine plus desmethylclomipramine plasma levels, measured as a 12-hour trough, should remain below 500 ng/mL to minimize toxicity risk.

^cRecommendation predates the FDA warning for dose-dependent QT prolongation

tion has been approved by the FDA for the treatment of OCD.

Following treatment response, antidepressant therapy should be continued for at least 1 to 2 years in order to reduce the risk of relapse.^{13,17} Ongoing symptoms, symptom severity and duration, and number of previous episodes should factor into the decision to discontinue pharmacotherapy.¹⁸ Withdraw antidepressants gradually, decreasing the dose by a maximum of 10% to 25% every 1 to 2 months while monitoring for return of OCD symptoms and antidepressant discontinuation syndrome.¹²

Patient Case 1

A 47-year-old patient was referred for psychiatric evaluation by the primary care provider. The patient displayed pathologic doubt coupled with compulsive checking behaviors. Obsessions involved fear that something terrible would happen, such as forgetting to turn off the oven before leaving home and accidentally burning down the house with their children still inside. Obsessional self-doubt was accompanied by feelings of guilt. The patient reported compulsively checking the oven before leaving the house and, upon driving away, frequently circling the neighborhood to drive back home to recheck the oven. These rituals occurred whenever leaving home and took several hours to perform each day. This resulted in disciplinary action at work because of frequent tardiness. The patient understood the behaviors were irrational. Past medical history included

dyslipidemia and insomnia. Medications included atorvastatin 20 mg by mouth once daily and ramelteon 8 mg by mouth once daily. Physical exam and vital signs were within normal limits. Labs were within normal limits except for a fasting low-density lipoprotein measured at 168 mg/dL. The patient reported an allergy to penicillin which caused hives during childhood.

The patient was diagnosed with OCD by the provider with a baseline Y-BOCS of 26, indicating severe OCD symptoms. The patient agreed to initiate CBT with exposure therapy and response prevention and pharmacotherapy. Sertraline was selected and started at 25 mg by mouth once daily and slowly titrated to 200 mg by mouth once daily. After 12 weeks of treatment, the patient tolerated the medication well. Obsessive-compulsive symptoms improved, but symptoms continued to impair the patient's daily functioning. The Y-BOCS was repeated and exhibited a 15% decrease in overall score.

SSRIs have relatively flat response curves when used for MDD, whereas treatment response for OCD is dose-related.¹³ Higher doses of SSRIs for OCD treatment may produce greater symptom reduction and greater response rates.¹² For patients tolerating SSRI therapy but with insufficient symptom relief, guidelines endorse increasing the SSRI dose to elicit a greater therapeutic response.^{8,12,17} The American Psychiatric Association (APA) guidelines¹² suggest the use of *occasionally prescribed* maximum doses that exceed FDA-approved maximum doses (Table 2). According to the APA guidelines,¹² the use of this high-dose antidepressant therapy should be considered if the patient is a rapid metabolizer or if 8 or more weeks of treatment at the maximum dose has produced an unsatisfactory response.

A meta-analysis¹⁹ of 9 randomized, placebo-controlled, fixed-dose trials examined the efficacy of low or medium SSRI doses versus high SSRI doses. High doses in this analysis were either at, or above, the maximum FDA approved daily dose. Trials ranged in duration from 8 to 13 weeks. The primary outcome assessed efficacy with change in Y-BOCS score using weighted mean difference. Compared to placebo, low, medium, and high doses significantly improved Y-BOCS scores, and the number needed to treat was found to be 6.3, 6.3, and 4.5, respectively. High doses produced greater efficacy than low (weighted mean difference = 2.1, CI = 1.0, 3.1, $P < .001$) or medium (weighted mean difference = 1.8, CI = 0.7, 2.9, $P = .001$) doses. Patients receiving high ($P < .001$), and medium ($P < .001$) doses were significantly more likely to drop out of the study because of adverse effects than placebo. A greater proportion of patients in the high-dose SSRI group dropped out of the study secondary to adverse effects than the low-dose SSRI group ($P = .03$).

Various trials have investigated high-dose therapy with individual SSRIs for the treatment of OCD. In these trials, high-dose therapy entails the use of antidepressants above their FDA approved maximum daily doses (Table 2).

A 12-week randomized, double-blind trial²⁰ evaluated high-dose sertraline therapy for OCD. Patients (N = 66) who did not respond during an initial 16-week trial of sertraline 50 to 200 mg/d were randomized to fixed dose (200 mg) or flexible dose (250-400 mg) groups for an additional 12 weeks. Treatment response was defined as a 25% or greater decrease in Y-BOCS score or a Clinical Global Impressions-Improvement (CGI-I) scale rating of 3 or less. No significant difference was found in response, with response rates for fixed dose and flexible dose groups of 33% and 40%, respectively ($P = .58$). The flexible dose sertraline group demonstrated significantly greater rate of change on regression analyses on the Y-BOCS ($P = .003$) and CGI-I ($P = .011$). Adverse effects were similar between groups with insomnia, diarrhea, nausea, headache, and fatigue occurring in at least 10% of patients in each group.

High-dose escitalopram was evaluated in 2 trials.^{21,22} A 16-week open-label trial²¹ examined high-dose (30 mg) and moderate-dose (20 mg) escitalopram in 23 patients. The high-dose group produced significantly more improvement on the Y-BOCS ($P = .039$); however, statistical significance was lost after controlling for differences in depression ($P = .955$) and anxiety ($P = .211$) scores between groups. Two patients required a dose reduction from 30 mg to 20 mg to alleviate adverse effects at the higher dose. A second 16-week open-label trial²² evaluated high-dose (up to 50 mg) escitalopram therapy. The primary outcome was change in Y-BOCS score from baseline. Patients (N = 64) not responding after 4 weeks of standard dosing (20 mg) continued treatment with high-dose escitalopram for an additional 12 weeks. The average dose was 33.8 mg/d. Eighty percent of patients demonstrated treatment response as defined by a 25% or greater reduction in Y-BOCS scores. Mean Y-BOCS score decreased from 29.6 to 16.2 over the course of 16 weeks ($P < .001$). Sexual dysfunction (31.8%) and dry mouth (12.1%) were the only reported adverse effects, and 1 patient experienced hypomania that resolved with dose reduction. No patients dropped out of the study because of adverse effects.

Case 1 is an example of a patient with OCD who is treated with a first-line antidepressant medication and concurrent CBT. Preliminary data suggest differences in response to SSRI therapy on the basis of OCD symptoms. Patients with aggressive, religious, or sexual symptoms may have a better pharmacologic response to SSRI treatment, whereas symmetry or hoarding symptoms may predict a poorer response. Serotonin is postulated to play a role in aggressive behavior, which may explain beneficial SSRI effects in patients with aggression. Conversely, dopamine is thought

to influence the symptoms of hoarding and symmetry, possibly explaining why these symptom domains respond less well to SSRIs.²³⁻²⁵ While a consideration, guidelines do not yet dictate treatment on the basis of these findings.

High-dose SSRI therapy produces serotonergic adverse effects that may be more likely to require mitigation strategies than standard dosing.²⁰⁻²² Gastrointestinal distress, agitation, insomnia, excessive sweating, and sexual dysfunction may commonly occur.¹² Using one-half of the recommended starting dose can minimize adverse effects, such as gastrointestinal distress and paradoxical anxiety.¹³ Insomnia from SSRIs can be managed by administering the medication in the morning and providing education on sleep hygiene. In addition to dose reductions, anticholinergics (eg, benztropine), alpha-2 receptor agonists (eg, clonidine), and alpha-1 receptor antagonists (eg, terazosin) have been used to decrease sweating severity.²⁶ Several strategies have been proposed for managing SSRI-induced sexual dysfunction, including waiting for spontaneous resolution, dose reductions, switching medications, the addition of bupropion, or the use of phosphodiesterase-5 inhibitors. Monitoring of high doses should also include evaluating patients for signs of serotonin syndrome, such as hyperactive bowel sounds, diaphoresis, clonus, and agitation.²⁷ If high-dose therapy is used for an older adult, monitor closely for adverse effects, including hyponatremia.

The patient in this case had a partial response to the FDA-approved maximum dose of sertraline following an adequate trial while also tolerating the medication well. Because this patient only achieved a partial response, consider further escalating to high-dose treatment (Table 2).¹² High-dose therapy should be continued for at least 6 weeks to assess patient response.¹² Because findings with high-dose therapy are mixed and duration of therapy is unclear in the long-term, periodic attempts to reduce to the standard dose should be considered.^{13,20} For patients who do not tolerate usual dosing well, an alternative strategy to high-dose therapy should be considered, such as switching to another first-line medication.²⁰

Patient Case 2

A 21-year-old college student arrived for a psychiatric evaluation. The patient's mother also attended the visit. The patient's compulsive hand washing was discovered during a visit with the dermatologist, and a referral to psychiatry was made. Fear of contamination and intrusive thoughts related to spreading germs was present along with comorbid tics. The patient reported that this began approximately 2 years ago, but the anxiety increased to a level that had never been experienced before. The patient attempted to hide this from family, but it became so time-consuming that secrecy was impossible, which further contributed to anxiety. The

TABLE 3: Suggested antipsychotic augmentation dosing for OCD^{28,29}

Antipsychotic ^a	Starting Dose (mg/d)	Suggested Dosing Range (mg/d)
Aripiprazole	2-5	15-30
Haloperidol	1-2	2-4
Olanzapine	2.5-5	5-10
Quetiapine	50-150	150-600
Risperidone	0.25-1	1-2

^aAntipsychotics are not FDA-approved for OCD.

patient's increased stress manifested as simple motor tics in the form of head jerks. The fear of germs and compulsive hand washing became so disruptive that the patient took a leave of absence from college. The patient understood the behavior was irrational but still feared the consequences of not performing the rituals. Past medical history was significant for seasonal allergies. Medications included loratadine 10 mg by mouth once daily. Vital signs and labs are within normal limits. Physical exam showed dry, red, cracked skin on both hands. The patient reported no known medication allergies.

The patient was diagnosed with OCD by the provider, with a Y-BOCS score of 23 (moderate symptoms) at baseline. Both CBT with exposure therapy and response prevention and pharmacotherapy were initiated. Fluoxetine was started at 20 mg and titrated to 40 mg in the morning after 2 weeks. The patient reported increased sweating with the 40 mg dosage. This resulted in the patient showering multiple times per day and experiencing an increase in anxiety related to the adverse effect. The fluoxetine was discontinued, and the patient agreed to try a different medication. Fluvoxamine extended-release was started and titrated to 300 mg once daily. Following 12 weeks of treatment at the 300 mg dosage, the Y-BOCS was scored at 19 (moderate symptoms). Fluvoxamine extended-release was gradually increased to 400 mg once daily. The patient did not tolerate the further dosage increase, and the dose was returned to the 300 mg dose. The prescriber recommended initiating an adjunctive antipsychotic. The patient was educated on the role of antipsychotics in OCD and common adverse effects. The patient agreed to a trial, and lurasidone 40 mg once daily with a meal was started.

Various antipsychotic medications have demonstrated anti-obsessional properties, but all are off-label for the treatment of OCD.^{12,28} Augmenting an antidepressant with an antipsychotic medication may be preferred over switching antidepressants if the patient has experienced a partial response to the antidepressant medication.¹² Antipsychotics are not recommended as monotherapy. Guidelines support the use of adjunctive antipsychotics if patients have not fully responded to SSRIs or clomipramine following trials of

sufficient duration.^{8,9} Aripiprazole and risperidone are recommended as first-line adjunctive pharmacotherapy.⁹ The onset of therapeutic effects occur over 2 to 4 weeks, and approximately one-third of treatment-resistant patients with OCD respond to antipsychotic therapy.^{6,29} Treatment duration is not clearly defined, but it has been suggested that antipsychotic therapy should be continued for at least 1 year following patient response to treatment.²⁹ Suggested antipsychotic dosing is provided in Table 3. Dosing is generally lower than doses for schizophrenia or bipolar mania management.^{28,29}

It may be prudent to monitor patients with OCD for new or worsening symptoms following antipsychotic initiation. Data suggest antipsychotics may produce or exacerbate obsessive-compulsive symptoms. Clozapine and olanzapine are most commonly implicated, with rates as high as 20% in clozapine-treated patients.³⁰ Serotonin-2A receptor antagonism is hypothesized as the most likely cause. First-generation antipsychotics, with predominantly antidopaminergic effects, are less commonly implicated.³¹ Aripiprazole, a partial dopamine-2 receptor agonist, has been shown to alleviate clozapine-induced OCD symptoms.³⁰ Evidence for antipsychotic-induced obsessive-compulsive symptoms is primarily limited to patients with schizophrenia or schizoaffective disorder.

A meta-analysis³² reviewed evidence for adjunctive antipsychotics for the treatment of OCD. Fourteen randomized, predominantly double-blind and placebo-controlled, trials were evaluated. Six antipsychotics were included: aripiprazole, haloperidol, olanzapine, paliperidone, quetiapine, and risperidone. Trials ranged from 4 to 16 weeks in length. Duration of antidepressant therapy before antipsychotic initiation ranged from 8 to 12 weeks. The primary outcome examined mean Y-BOCS change in total score. The pooled antipsychotic group significantly reduced Y-BOCS score as compared to placebo (Hedges $g = -0.64$, 95% CI = $-0.87, -0.41$; $P \leq .01$). When evaluated individually, aripiprazole ($P \leq .01$), risperidone ($P = .02$), and haloperidol ($P = .02$) each significantly differed from placebo, whereas olanzapine, paliperidone, and quetiapine did not. Average risperidone and aripiprazole doses across trials^{32,33} were 0.5 to 2.2 mg and 10 to 15 mg, respectively. Mean reduction in Y-BOCS scores were 6.1 to 8.7 for risperidone and 6.6 to 7.1 for aripiprazole.³³ Limitations include few available studies evaluating antipsychotic augmentation; for example, only 2 aripiprazole trials are cited in the aforementioned analysis. It should be noted that trials in this area are limited by small sample sizes and short study duration, limiting the ability to assess long-term outcomes related to efficacy and tolerability.

Case 2 illustrates a patient with OCD who is treated with an SSRI and started on antipsychotic therapy. While antipsychotic medications remain off-label for OCD, treatment guidelines support their use for antidepressant augmenta-

tion.^{8,9} Consider antipsychotic treatment if high-dose antidepressant therapy and CBT are not tolerated or fail to adequately produce response.¹⁷ The choice of antipsychotic in this patient case warrants further review. No controlled trials have evaluated adjunctive lurasidone for the treatment of patients with OCD, so it should be replaced with an agent that has research supporting its use. Augmentation with risperidone, aripiprazole, haloperidol, quetiapine, and olanzapine are cited by treatment guidelines; however, systematic reviews most strongly support aripiprazole or risperidone use.^{8,9,17,32,33} Risperidone augmentation was associated with sedation (30%-35%), dry mouth (20%), and increased appetite (15%) in OCD trials, whereas aripiprazole augmentation was associated with restlessness (43.7%), insomnia (12.5%), and nausea (6.3%).³⁴⁻³⁶

Antipsychotic augmentation may be especially useful in patients with comorbid tic disorders. In a meta-analysis examining antipsychotic augmentation for treatment refractory OCD, patients with comorbid tic disorders appeared more likely to benefit. The absolute risk difference in the presence of comorbid tics was 0.43 (95% CI = 0.19, 0.68) versus the absence of comorbid tics at 0.17 (95% CI = 0.07, 0.27). The number needed to treat for patients with or without comorbid tics was 2.3 and 5.9, respectively.³⁷

In this case, aripiprazole may be preferred secondary to its lower risk of weight gain and hyperprolactinemia; in addition, less sedation may help avoid interference with studies once the patient resumes schooling.^{28,38} Consider starting at a low dose to minimize activating adverse effects. Titrate the dose to 10 to 15 mg on the basis of response and tolerability as these doses were evaluated in clinical trials.^{32,33} Response to therapy should be monitored by week 4 and, if symptom response has occurred, the patient should be educated on potential long-term adverse effects. Following response to therapy, continue aripiprazole for at least 1 year.²⁹ Limited data suggest relapse rates are high upon antipsychotic discontinuation, and close monitoring and frequent follow up are warranted if discontinuation is pursued.³⁹ The Y-BOCS should be used at baseline and periodically throughout therapy to track response to treatment. Monitor for potential adverse effects to aripiprazole, such as restlessness, insomnia, and nausea.²⁸ To minimize insomnia, aripiprazole can be taken in the morning. Monitor metabolic parameters periodically.⁴⁰ The Abnormal Involuntary Movement Scale should be used at least annually to assess for the presence of tardive dyskinesia.⁴¹ Aripiprazole is a CYP3A4 and 2D6 substrate; therefore, monitor for potential CYP inhibitor and inducer interactions. Other first-line antidepressants for OCD, paroxetine and fluoxetine, are strong CYP2D6 inhibitors and may significantly increase aripiprazole serum concentrations. Administer half of the usual aripiprazole dose when using these medications.²⁸

Patient Case 3

A 20-year-old, diagnosed with OCD 2 years ago, presented to the emergency department with a parent. During childhood, the patient had a history of counting rituals that had to be performed prior to starting tasks. Two years ago, the patient developed a fear of germs. The patient washed their hands dozens of times per day, and records from dentistry indicated damage caused to the tooth enamel from excessive teeth brushing. The patient no longer left home and expressed suicidal thoughts. Past medication trials included paroxetine, fluoxetine, and fluvoxamine. Home medications included sertraline 200 mg once daily and clomipramine 75 mg twice daily. Higher doses of sertraline were not tolerated secondary to tremor and agitation. Two months ago, the patient's combined clomipramine and desmethylclomipramine level was 125 ng/mL (guidelines suggest maintaining less than 500 ng/mL) and Y-BOCS score was 27 (severe symptoms).

The patient was admitted to inpatient psychiatry where both medications were continued and risperidone 0.25 mg at bedtime was initiated. Risperidone was titrated to 1 mg twice daily. Following a 1-week inpatient admission, the suicidal ideations had subsided, and the patient was subsequently discharged. All medications were continued at discharge, and the patient was enrolled in a partial hospitalization program to address continued contamination fears and excessive hand washing. A repeat Y-BOCS failed to show substantial improvement. Memantine augmentation was ordered for the patient.

Glutamate-modulating medications continue to generate interest for the treatment of OCD.⁴² Disturbances in glutamatergic neurotransmission in corticostriatal-thalamocortical pathways have been described in patients with OCD.⁴³ While several medications have been investigated such as riluzole, topiramate, d-cycloserine, and N-acetylcysteine, memantine remains one of the most widely studied adjunctive glutamatergic medications for OCD treatment.^{12,42} Memantine is an uncompetitive N-methyl-D-aspartate receptor antagonist.²⁸

Memantine has been studied in several OCD clinical trials, including 4 randomized, controlled trials.⁴³⁻⁴⁶ Three trials evaluated memantine-augmented serotonin reuptake inhibitors, whereas 1 trial examined memantine for obsessive compulsive symptoms in patients with bipolar disorder who were taking mood stabilizing medications. Trials ranged from 8 to 16 weeks in duration, and sample sizes in each trial were less than 40 patients. Memantine dosing in one trial was 5 to 10 mg, whereas other trials evaluated 20 mg. Only 1 trial evaluated patients who were deemed treatment refractory. All studies used the Y-BOCS as the primary outcome. A meta-analysis⁴⁷ evaluating all 4 trials found the

change in Y-BOCS score between memantine and placebo was 7.76 (95% CI = 2.58, 12.95, $P < .001$).

Several limitations must be considered when interpreting the memantine augmentation data. Trials consisted of small sample sizes and relatively short durations. The majority of patients with OCD have at least 1 psychiatric comorbidity; however, patients with comorbidities were excluded from all but 1 of these trials. Only 1 trial evaluated patients with treatment refractory OCD; therefore, the results may not be generalizable to the population most likely to be considered for adjunctive memantine.⁴³⁻⁴⁶ Commentary⁴⁸ related to these trials has been published and is critical of study methodologies. The author⁴⁸ stated all 4 trials were conducted in the same country, potentially limiting generalizability, and internal validity was affected by several factors, including the lack of clarity surrounding patient dropouts in the studies.

Case 3 depicts a patient with OCD who has failed multiple first-line medications and is currently treated with an SSRI with adjunctive clomipramine and risperidone. High-dose SSRI therapy was tried but poorly tolerated. Various treatment guidelines regard memantine as either a second-line adjunctive option or as an unproven approach for managing OCD.^{8,9} With other treatment strategies untried, memantine augmentation may not be indicated for this particular patient.

Several treatment strategies can be considered at this time. CBT with exposure therapy and response prevention is a first-line treatment strategy. This would be a reasonable treatment strategy to explore as the combination of CBT and antidepressants is more effective than either alone.^{9,12} The patient was recently placed on a risperidone 2 mg dose. Maximal effects of this dosage increase have likely not occurred over the past week, and continued monitoring for adverse effects and treatment response at this new higher dose is prudent. Switching to aripiprazole augmentation is a potential option if risperidone is ineffective or poorly tolerated. A third potential treatment avenue would be to maximize clomipramine therapy. The patient currently takes 150 mg/d, resulting in a plasma level of 125 ng/mL. The dose can be titrated up to a maximum of 250 mg/d.²⁸ Monitor plasma levels to ensure the combined clomipramine and desmethylclomipramine level remains lower than 500 ng/mL to minimize the risk of seizures and conduction abnormalities.¹² Avoid simultaneous changes to the medication regimen in order to assess the outcome of each adjustment. Consideration should be given to these approaches prior to memantine augmentation.

Conclusion

The treatment of OCD includes the use of first-line SSRI antidepressants. SSRIs produce response rates of approxi-

mately 60%; therefore, strategies beyond first-line interventions are needed to achieve response, and ultimately remission, for many patients with OCD. High-dose SSRI therapy and adjunctive antipsychotics are broadly supported by treatment guidelines. Limited data suggest adjunctive memantine may be beneficial; however, additional research to support its role in the management of OCD is needed before it can be routinely recommended ahead of other evidence-based strategies.

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