

Treatment-resistant



OCD:

There's more we can do

Augmentation strategies may help patients who don't respond to first-line treatments

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Mr. S, age 30, transfers to your practice and shares that he was first diagnosed with obsessive-compulsive disorder (OCD) at age 10. He currently worries about whether he may have offended people by using the wrong words in his emails and he apologizes excessively. He fears that his body odor disturbs other people, and he sprays room freshener every time he exits a room. To measure the severity of his current symptoms, you complete the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Mr. S's Y-BOCS score is a 32 out of a maximum of 40, indicating severe OCD. Previously, he has received trials of adequate doses of 2 selective serotonin reuptake inhibitors (SSRIs; fluoxetine and sertraline) and currently is taking clomipramine, 100 mg twice daily. However, he still is experiencing substantial obsessions and compulsions that interfere with his relationships with his friends and family members.

Treatment-resistant OCD can be a debilitating condition. Diagnostic clarity is crucial to fully elicit symptoms and identify comorbid conditions in order to develop practical, evidence-based treatment strategies and improve the patient's and family's quality of life. In this article, we delineate first-line strategies for treatment-resistant OCD and then review augmentation strategies, with an emphasis on glutamate-modulating agents.

Making the diagnosis

The diagnosis of OCD is made when a patient meets DSM-5 criteria for the presence of obsessions and/or compulsions, which are defined as unwanted, distressing, intrusive, recurrent thoughts or images (obsessions)





Obsessive-compulsive disorder

Clinical Point

The hidden nature of symptoms and reinforcement from performing a compulsion contribute to sustained illness



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Table 1

Comorbid conditions common in OCD

Attention-deficit/hyperactivity disorder
Body dysmorphic disorder
Dermatillomania
Eating disorders
Generalized anxiety disorder
Major depressive disorder
Panic disorder
Parent-child relational problems
Social phobia
Tic disorders
Trichotillomania
OCD: obsessive-compulsive disorder

and repetitive behaviors or mental acts (compulsions).¹ OCD is considered a chronic waxing and waning disorder; stress and lack of sleep lead to worsening symptoms. The hidden nature of symptoms and the reinforcement provided by the reduction in anxiety after performing a compulsion contribute to sustained illness. Eliciting symptoms from patients may be challenging due to the shame they may feel. When reviewing symptoms on the Y-BOCS, it is helpful to preface questions with statements such as “Many people report excessive concern or disgust with...” to help the patient feel understood and less anxious, rather than using direct queries, such as “Are you bothered by...?”

Consider comorbid conditions

After making the initial diagnosis of OCD, it is important to assess whether the symptoms are better accounted for by another condition, and whether comorbid conditions are present (Table 1).

CASE CONTINUED

Ruling out other diagnoses

In the course of Mr. S’s evaluation, you rule out a psychotic disorder because he has insight that his behaviors may not be necessary to combat his fears. You also rule out a mood disorder with obsessive features. Although Mr. S admits he is frustrated by a lack of relief from medication, he denies experiencing any

sustained periods of mania, low mood, or suicidal thoughts. He does endorse excessive guilt for contaminating people’s homes and poor concentration at work because he often is distracted by his fears that he has offended his colleagues.

Initial treatment: CBT

Cognitive-behavioral therapy with exposures and response prevention (from here on referred to as CBT) has been established as a first-line, evidence-based treatment for OCD in both children and adults.^{2,3} For patients with treatment-resistant OCD, intensive daily CBT in a partial hospitalization or inpatient setting that is a tailor-made, patient-specific program is one of the most effective treatments, with response rates of up to 70%.⁴⁻⁸ CBT’s advantages over medication include lower relapse rates and no known adverse effects. Unfortunately, CBT is underused⁹⁻¹¹ due in part to a shortage of trained clinicians, and because patients may favor the ease of taking medication over the time, effort, and cost involved in CBT.

First-line pharmacologic options for treating OCD are SSRIs and clomipramine, as supported by multiple randomized controlled trials (RCTs), meta-analyses, expert guidelines, and consensus statements (Table 2,^{2,12-14} page 14). No significant difference has been found among SSRIs for the treatment of OCD in a review of 17 studies that included more than 3,000 patients.¹⁵ Treatment with SSRIs or clomipramine is effective for 50% to 60% of patients.¹⁶ Many clinicians view the combination of an SSRI and CBT as the treatment of choice for OCD.²

CASE CONTINUED

Reluctance to engage in CBT

To determine the next course of action, you review Mr. S’s treatment history. He has received adequate doses of 2 SSRIs and currently is taking clomipramine, 100 mg twice daily. He recently began CBT, which includes homework to help face his fears; however, Mr. S is reluctant to complete the exposure assignments, and after pausing for a few seconds as he tries to resist sending an apology

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Obsessive-compulsive disorder

Clinical Point

Almost half of adults with OCD respond to CBT and/or a selective serotonin reuptake inhibitor

Table 2

First-line treatments for obsessive-compulsive disorder

Treatment	Dose	Comments
Cognitive-behavioral therapy with exposure and response prevention	Average 12 to 20 sessions	To find local therapists with expertise in this modality, search the International OCD Foundation web site: https://iocdf.org
Fluoxetine	20 to 80 mg/d	Monitor for activation, insomnia. May lead to vivid dreams
Fluvoxamine	Up to 200 mg/d in children; 300 mg/d in adults in divided doses	Monitor for disinhibition/poor judgement
Sertraline	Up to 200 mg/d in children and adults	Take with food. May lead to GI discomfort
Escitalopram	Up to 40 mg/d	May lead to drowsiness and weight gain
Paroxetine	Start at 20 mg/d, increase in 10-mg intervals; maximum dose 60 mg/d	May lead to drowsiness and weight gain. Nonlinear pharmacokinetics. Most difficult to discontinue
Citalopram	Up to 40 mg/d	Higher doses require ECG monitoring
Clomipramine	Up to 300 mg/d in divided doses	Monitor ECG for QTc prolongation at baseline and every 6 months. IV clomipramine may be more effective than oral clomipramine

Source: References 2,12-14
ECG: electrocardiography; GI: gastrointestinal; OCD: obsessive-compulsive disorder

email to his coworkers, he then returns to his compulsive behavior.

Facing treatment resistance

Although currently there isn't a cure to resolve all traces of OCD, the goal of treatment is to decrease distress, interference, and the frequency of symptoms to a minimal level such that only the patients themselves are aware of symptoms. In broad terms, "response" has been defined as a decrease in symptoms, and "remission" has been defined as minimal symptoms after treatment.

Close to half of adults treated for OCD respond well to standard-of-care treatment (CBT and/or an SSRI), while the other 50% are considered partial responders or nonresponders.² For patients with OCD, researchers often define "treatment response" as a $\geq 25\%$ reduction in symptom severity score on the Y-BOCS. Approximately 30% of adults with OCD do not respond substantially to the first-line treatments, and even those who are defined as "responders" in research

studies typically continue to have significant symptoms that impact their quality of life.² In children, a clinical definition for treatment-refractory OCD has been presented as failing to achieve adequate symptom relief despite receiving an adequate course of CBT and at least 2 adequate trials of an SSRI or clomipramine.¹⁷ In the Pediatric OCD Treatment Study (POTS) trial, $>46\%$ of youth did not achieve remission from their OCD symptoms, even after receiving evidence-based care provided by experienced clinicians (combined treatment with CBT and an SSRI).¹⁸

Challenges in psychotherapy

Compassion is a key element in developing rapport with patients to help them face increasingly more challenging exposures. Making OCD the problem, not the person, is an essential element in helping patients move forward. Some clinicians may become frustrated with patients when treatment is not moving along well, referring to resistance, denial, or sabotage. According to March and Mulle,¹⁹ these terms lack the

Table 3

Mechanism of action and common uses for alternative agents

Agent	Mechanism	Common uses
<i>N</i> -acetylcysteine	Role in the release of glutamate by modulating the cysteine-glutamate antiporter	Antioxidant to treat acetaminophen overdose
Memantine	Low-affinity antagonist of extrasynaptic NMDA glutamate receptors	Delay cognitive decline in patients with Alzheimer's disease
Ketamine	More potent noncompetitive antagonist of the NMDA receptor than memantine	Anesthetic. Drug of abuse
Topiramate	Directly inhibits AMPA/kainate glutamate receptors	Prevent seizures and headaches
Lamotrigine	Reduce glutamate outflow through inhibition of certain presynaptic voltage-gated sodium channels	Antiepileptic and mood stabilizer
D-cycloserine	Agonist at the glycine site on the NMDA receptor	Animal studies on learning, eg, fear extinction

AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA: *N*-methyl-D-aspartate

recognition and compassion that exposures are inherently difficult.¹⁹

Another challenge for therapists is if the patient's presenting symptoms are personally offensive or a sensitive topic. For example, a therapist who is disgusted by public restrooms will find it difficult to tolerate the risks associated with exposure to germs and support a patient in touching objects in the restroom. Therapists also may be challenged when the patient's fears align with the therapist's religious beliefs. In these situations, consider transferring care to another therapist.

Family members need to learn about the nature of the illness and their roles in helping patients improve. Family members may unknowingly enable symptoms or criticize patients for their lack of motivation, which can lead to conflict in the home. Family dysfunction can in turn worsen OCD symptoms.

The most likely cause of lack of response to therapy is inexpert CBT.¹⁹ Deep breathing and relaxation training have been used as an active placebo in studies²⁰; in a meta-analysis examining the effective components of CBT, studies that added relaxation training were not more effective than those that employed exposures alone.²¹ Patients receiving CBT should be able to articulate the hierarchical approach used to gradually face their fears.

Pharmacologic augmentation strategies

Selective serotonin reuptake inhibitors.

While most OCD research trials have assessed SSRIs in 12-week studies, clinicians may consider extending SSRI treatment for an additional 12 weeks for nonresponders because some patients will continue to make gains. In the past, it was generally believed that higher doses of SSRIs are needed for treating OCD than for treating major depressive disorder. For instance, greater improvement was seen with 250 to 400 mg/d of sertraline compared with 200 mg/d²² and with escitalopram after an increase of dose up to 50 mg/d.²³ However, more recently, this notion of higher doses being necessary for treatment response has been called into question. For example, a study of escitalopram found similar responses to 10 mg/d vs 20 mg/d after 24 weeks.²⁴ A meta-analysis of adult studies of SSRIs for OCD supported higher doses as being more effective, but noted that the drop-out rate from treatment was greater in patients treated with higher doses.²⁵ As a note of caution, long-term, high-dose maintenance therapy increases the risk of adverse reactions.²⁶

Following a failed treatment with a first SSRI, it remains debatable as to what ought to be the second pharmacologic treatment. Although clomipramine is often reserved

Clinical Point

The most likely cause of lack of response to therapy is inexpert cognitive-behavioral therapy



Obsessive-compulsive disorder

Clinical Point

Some clinicians employ a strategy of combining clomipramine with an SSRI, while monitoring for serotonin syndrome

Table 4

Literature summary of augmentation strategies

Beneficial as augmentation to SSRI	Mixed results	Not beneficial as augmentation or monotherapy	Helpful early in treatment
Memantine	<i>N</i> -acetylcysteine	Benzodiazepines	D-cycloserine
Lamotrigine	Topiramate		
	Ketamine		

SSRI: selective serotonin reuptake inhibitor

for treatment after 2 failed trials of an SSRI due to its greater risk of adverse effects, in an open-label study, switching from an SSRI to clomipramine led to greater response than switching from one SSRI to another.²⁷ On the other hand, while meta-analyses have reported greater treatment effect for oral clomipramine than for SSRIs, direct head-to-head comparisons have not supported this notion.²⁸ To get the best of both worlds, some clinicians employ a strategy of combining clomipramine with an SSRI, while monitoring for adverse effects and interactions such as serotonin syndrome.²⁹⁻³¹

Benzodiazepines. Although benzodiazepines are useful for brief treatment of an anxiety disorder (eg, for a person with a fear of heights who needs to take an airplane),³² they have not been shown to be effective for OCD³³ or as augmentation to an SSRI.³⁴

***N*-acetylcysteine (NAC).** Two RCTs of adults with OCD who received adjunctive NAC, 3 g/d in divided doses, found no significant difference in the treatment arms by the conclusion of 16 weeks—either both groups improved, or both groups failed to improve.^{35,36} In a 10-week study of patients with moderate to severe OCD symptoms, NAC, 2 g/d, as augmentation to fluvoxamine, 200 mg/d, showed a significant time x interaction in the treatment group.³⁷ No follow-up information is available, however.

In a multicenter RCT of NAC given to children and adolescents with OCD as augmentation to citalopram, symptoms decreased and the quality-of-life score improved, with a large treatment effect size in the NAC group.³⁸ However, in a study aimed at examining NAC in youth with

Tourette syndrome, OCD symptoms were measured as a secondary outcome and there was no benefit of NAC over placebo.³⁹

Memantine. Four 8- to 12-week RCTs in adults with OCD favored adjunctive memantine, 20 mg/d, taken with an SSRI, over placebo.⁴⁰⁻⁴³ A small study suggests that patients with OCD may be more likely to respond to memantine than patients with generalized anxiety disorder.⁴⁴ Case reports have noted that memantine has been beneficial for pediatric patients with refractory OCD.⁴⁵

Topiramate. Three 12-week RCTs examined topiramate augmentation at 100 to 400 mg/d in patients with OCD who had failed at least 1 previous trial of an SSRI. The earliest study was most encouraging: Y-BOCS scores decreased by 32% in the topiramate group but by only 2.4% in the placebo group.⁴⁶ However, the other 2 studies found no difference in the final OCD symptom severity score between active treatment and placebo groups,^{47,48} and the use of topiramate, particularly at higher doses, was limited by its adverse effects.

Lamotrigine. Initially, lamotrigine augmentation of SSRIs in OCD did not appear to be helpful.⁴⁹ More recently, several case studies reported that lamotrigine, 100 to 200 mg/d, added to paroxetine or clomipramine, resulted in dramatic improvement in Y-BOCS scores for patients with long-standing refractory symptoms.^{50,51} In a retrospective review of 22 patients who received augmentation with lamotrigine, 150 mg/d, 20 had a significant response; the mean decrease in Y-BOCS score was 67%.⁵²

Finally, in a 16-week RCT, lamotrigine, 100 mg/d, added to an SSRI led to a significant decrease in both Y-BOCS score and depressive symptoms while also improving semantic fluency.⁵³

Ketamine. Ketamine is drawing increased attention for its nearly instantaneous anti-depressant effect that lasts for up to 2 weeks after a single infusion.⁵⁴ In a study of 15 medication-free adults with continuous intrusive obsessions, 4 of 8 patients who received a single IV infusion of ketamine, 0.5 mg/kg, met the criteria for treatment response (>35% reduction in Y-BOCS score measured 1 week later); none of the patients who received a placebo infusion of saline met this criteria.⁵⁵ A small open-label trial of 10 treatment-refractory patients found that an infusion of ketamine, 0.5 mg/kg, was beneficial for comorbid depression but had only a minimal effect on OCD symptoms measured 3 days post-infusion.⁵⁶ A short-term follow-up on these patients revealed dysphoria in some responders.⁵⁷

D-cycloserine. The idea of using a pharmacologic agent to increase the speed or efficacy of behavioral therapy is intriguing. Proof of concept was demonstrated in a study that found that giving D-cycloserine prior to computerized exposure therapy significantly improved clinical response in patients with acrophobia.⁵⁸ However, using this approach to treating OCD netted mixed results; D-cycloserine was found to be most helpful during early stages of treatment.^{59,60}

Table 3 (page 15) outlines the mechanisms of action and common uses for NAC, memantine, ketamine, topiramate, lamotrigine, and D-cycloserine. *Table 4 (page 16)* summarizes the literature on the

Related Resources

- Yale-Brown Obsessive-Compulsive Scale. <https://iocdf.org/wp-content/uploads/2014/08/Assessment-Tools.pdf>.
- The International OCD Foundation. <https://iocdf.org>.

Drug Brand Names

Citalopram • Celexa	Lamotrigine • Lamictal
Clomipramine • Anafranil	Memantine • Namenda
Escitalopram • Lexapro	Paroxetine • Paxil
Fluoxetine • Prozac	Sertraline • Zoloft
Fluvoxamine • Luvox	Topiramate • Topomax
Ketamine • Ketalor	

efficacy of some of the augmentation strategies for treating OCD described in this article.

Alternative strategies

Augmentation strategies with neuroleptics,⁶¹ transcranial magnetic stimulation,⁶² and deep brain stimulation⁶³ have recently been reviewed. Space limitations preclude a comprehensive review of these strategies, but in a cross-sectional study of augmentation strategies in OCD, no difference was found in terms of symptom severity between those prescribed SSRI monotherapy or augmentation with neuroleptics, benzodiazepines, or antidepressants.⁶⁴

CASE CONTINUED

Progress in CBT

Mr. S agrees to a trial of NAC as an augmentation strategy, but after 8 weeks of treatment with NAC, 600 mg twice daily, his Y-BOCS had declined by only 2 points. He also complains of nausea and does not want to increase the dose. You discontinue NAC and opt to further explore his reaction to CBT. Mr. S shares that he has been seeing his psychologist only once every 3 weeks because he does

Clinical Point

Some evidence suggests adding lamotrigine to an SSRI can decrease Y-BOCS scores in patients with OCD

Bottom Line

It is unrealistic to expect OCD symptoms to be cured. Many 'treatment-resistant' patients have not received properly delivered cognitive-behavioral therapy, and this first-line treatment modality should be considered in every eligible patient, and augmented with a selective serotonin reuptake inhibitor (SSRI) when needed. Glutamatergic agents, in turn, can augment SSRIs.



Obsessive-compulsive disorder

Clinical Point

Using D-cycloserine may help to improve OCD patients' response to behavioral therapy during early stages of treatment

not want to miss work. You encourage him to increase to weekly CBT sessions, and you obtain his permission to contact his therapist and his family members. Fortunately, his therapist is highly qualified, but unfortunately, Mr. S's father has been sending him multiple critical emails about not advancing at his job and for being "lazy" at work. You schedule a session with Mr. S and his father. Great progress is made after Mr. S and his father both share their frustrations and come to understand and appreciate each other's struggles. Four weeks later, after weekly CBT appointments, Mr. S has a Y-BOCS of 18 and spends <2 hours/d checking emails for errors and apologizing.

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