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Dr. Bystritsky: Diagnostic dilemmas with OCD and other anxiety disorders

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Treatment-resistant OCD:

Options beyond first-line medications

Adjunctive agents, psychotherapy, neuromodulation may help refractory symptoms

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Obsessive-compulsive disorder (OCD) is marked by recurrent and persistent anxiety-provoking thoughts (obsessions) accompanied by repetitive behaviors (compulsions) that focus on alleviating distress caused by obsessive thoughts. Although patients recognize the obsessions and compulsions are unreasonable, these thoughts and behaviors remain time-consuming and impair function. Even when they appropriately identify and treat OCD, clinicians often face "treatment-resistant" (or "treatment-refractory") patients who do not respond adequately to standard therapies (***Box, page 46***).[1] Several factors contribute to treatment resistance, including those related to the patient, the environment, the clinician/health system, and pathology (***Table 1, page 48***).[2] An estimated 10% to 40% of patients with OCD are treatment-resistant.[2]

This article discusses the range of options for addressing resistant OCD, including augmenting first-line treatments with pharmacotherapy, psychotherapy, or reversible or irreversible forms of neuromodulation.

First-line pharmacotherapy

Clomipramine or a selective serotonin reuptake inhibitor (SSRI) are considered first-line treatments for OCD. Although some evidence indicates that clomipramine may have greater efficacy than SSRIs, its poor tolerability and potential lethality in overdose make it a less practical first choice in treatment-naïve patients.[3,4] SSRIs generally are well tolerated and have a favorable safety profile. Nearly all SSRIs have randomized clinical trials (RCTs) and FDA indications that support their use in OCD. SSRI choice may be guided by patient or prescriber preference because

Treatment-resistant OCD

Box

Defining treatment resistance in obsessive-compulsive disorder

Treatment resistance generally refers to lack of sufficient improvement despite multiple adequate and appropriate treatment trials. However, there are no universally accepted definitions or metrics of treatment resistance, and often it is operationally defined. For mood disorders, it may be defined by failure to remit or respond clinically (50% reduction in symptoms) despite ≥2 adequate antidepressant trials or failure to respond clinically despite adequate medication trials across several neurotransmitter classes. The terms treatment resistant and treatment refractory are synonymous; they refer to the same phenomenon and are used interchangeably in the literature. Including the terms "remission" and "recovery" when judging treatment efficacy for anxiety disorders can be limiting because of the chronic and often unrelenting nature of these conditions.

One review proposed categorizing obsessive-compulsive disorder treatment response into several stages along a spectrum, ranging from complete recovery (or remission) to full or partial response to non-response (or completely refractory).[1] However it is defined, treatment resistance in anxiety disorders likely is characterized by minimal restoration of function despite several appropriate treatment exposures.

Clinical Point

In OCD higher SSRI doses typically are required to achieve response or remission

no evidence suggests that 1 SSRI is superior to another for treating OCD.[5] In contrast to major depressive disorder, in OCD there is a dose-response relationship for SSRI treatment; higher doses typically are required to achieve response or remission.[6,7]

Augmentation and other options

Patients who have not responded to at least 2 adequate trials of first-line medications may benefit from an augmentation strategy or treatment with an unconventional agent. Such cases should be managed by a specialist who has experience in treating OCD and with careful consideration of potential risks of these interventions.

Evidence suggests the following pharmacotherapies may effectively treat OCD and may be warranted for treatment-resistant patients.

Serotonergic agents

Supratherapeutic SSRI doses. Evidence suggests that supratherapeutic doses of SSRIs may be effective, which may be a logical first step when treating patients already taking an SSRI who have not responded. In a multi-center, double-blind study comparing sertraline, 200 mg/d, to sertraline, 250 to 400 mg/d, the latter group showed significantly greater symptom improvement.[8] Citalopram may not be suitable for this approach because of the recent FDA announcement regarding dose-dependent QTc prolongation associated with this medication.[9]

Serotonin-norepinephrine reuptake inhibitors (SNRIs). In the only double-blind, placebo-controlled study of venlafaxine for OCD, the drug was not significantly more effective than placebo.[10] This study was small (N = 30). There are sufficient positive results from open-label and blinded comparator studies that venlafaxine generally is accepted as an effective and well-tolerated treatment for OCD at doses ≥225 mg/d.[11]

Duloxetine also may be effective in treating OCD. One case series reported improvement in 3 of 4 SSRI nonresponders who were switched to this medication and rapidly titrated to 120 mg/d.[12]

Clomipramine/SSRI augmentation. For patients who have not responded to an SSRI, several open-label trials support adding clomipramine.[13] Conversely, SSRI augmentation for patients who have not adequately responded to clomipramine may be effective.[14] With any dual therapy with serotonergic agents, monitor patients for signs and symptoms of serotonin syndrome.

IV clomipramine. By bypassing first-pass metabolism, IV clomipramine rapidly achieves high plasma levels. In a double-blind, placebo-controlled study of 54 OCD patients who were nonresponsive to oral

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clomipramine, IV clomipramine was more effective than placebo.[15] An additional study found IV clomipramine is more effective when pulse loaded than when titrated gradually.[16]

Pindolol. The beta blocker pindolol acts as an antagonist of presynaptic 5-HT1A autoreceptors, increasing serotonergic signaling. A small double-blind, placebo-controlled trial (N = 14) found a significant decrease in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score with pindolol augmentation, 2.5 mg, 3 times daily, among patients who did not respond to ≥3 serotonin reuptake inhibitor (SRI) trials.[17] Pindolol augmentation showed modest effects in 2 open-label studies.[18,19] However, another small double-blind, placebo-controlled study (N = 15) found no difference between placebo and fluvoxamine augmented with pindolol.[20]

Ondansetron. A 5-HT3 receptor antagonist, ondansetron is used primarily as an antiemetic but has been shown to have anxiolytic properties in animal studies. In an open-label study of 8 patients with non–treatment refractory OCD, 3 achieved clinical response (at least 35% reduction in Y-BOCS score) with ondansetron monotherapy dosed at 1 mg, 3 times daily.[21] In a subsequent single-blind trial with 14 treatment-resistant patients, 9 responded (at least 25% reduction in Y-BOCS score).[22]

Other medications

Antipsychotics. Most studies examining antipsychotic monotherapy for OCD have been negative. One exception was a small, open-label trial of aripiprazole monotherapy (N = 8) that found modest efficacy among non–treatment refractory patients.[23] Augmentation with antipsychotics, however, has been well studied and there is good evidence of efficacy for this approach. Double-blind, placebo-controlled studies have supported the efficacy of augmenting SRIs with haloperidol, risperidone, olanzapine, quetiapine, and aripiprazole.[24-26] Several case reports suggest ziprasidone may be an effective SRI adjunct, but 1 retrospective study found it was inferior to quetiapine.[27]

Benzodiazepines. Case reports present positive effects of clonazepam and alprazolam for OCD, but double-blind, placebo-controlled trials for monotherapy or adjunctive clonazepam have been negative.[28,29] Furthermore, cognitive impairment and potential for dependence associated with benzodiazepines weigh against their use in OCD.

Opioids. A double-blind, placebo-controlled crossover study of 23 patients with treatment-refractory OCD found once-weekly oral morphine added to patients' current regimen significantly reduced Y-BOCS score vs placebo. Patients received 30 mg the first week and 15 to 45 mg the next week, depending on response or side effects.[30] A case report and a small open-label trial support the efficacy of tramadol, a weak agonist of the μ opioid receptor and an inhibitor of serotonin and norepinephrine transporters, as monotherapy and as an adjunct to fluoxetine.[31,32] Because patients with OCD may be particularly vulnerable to dependence and intentional or accidental overdose via opioid/benzodiazepine combinations, evaluate the risks and benefits before initiating an opioid.

Psychostimulants. Sparse but good evidence supports the efficacy of dextroamphetamine monotherapy for OCD.[33,34] There are no positive studies of methylphenidate and several case reports of methylphenidate-induced OCD symptoms.[35]

N-methyl-D-aspartate (NMDA) antagonists. Increased glutamatergic neurotransmission has been implicated in the pathophysiology of OCD, which suggests a possible role for glutamate receptor antagonists. In an open-label trial, memantine, an NMDA antagonist used primarily to treat dementia, was associated with clinical response (>25% reduction in Y-BOCS scores) in 6 of 14 patients with treatment-refractory OCD.[36] Several case reports and an open-label trial support the efficacy of riluzole—which is indicated for treating amyotrophic lateral sclerosis—as an adjunct for

Clinical Point

Studies show augmenting SRIs with antipsychotics is effective for OCD

Treatment-resistant OCD

Clinical Point

One benefit of CBT over pharmacotherapy for OCD is that effects persist after treatment is terminated

Table 1

Factors that contribute to treatment resistance in obsessive-compulsive disorder

Patient
Disease severity
Medical comorbidity
Psychiatric comorbidity (mood, personality, and/or substance use disorders)
Treatment nonadherence
Cultural factors
Environment
Childhood stressors (trauma, abuse)
Long-term persistent stressors (psychosocial, occupational, financial)
Life stages
Clinician/health system
Lack of knowledge in primary care (brief treatment duration, subtherapeutic dosing)
Lack of psychotherapeutic training
Limited doctor-patient relationship (eg, availability/cost of treatment)
Pathology-related
Underlying disease pathophysiology (largely unknown): • Multiple neurotransmitter system interactions • Polygenetic influences (genetic load) • Gene-environment interactions • Neural circuits (cortical and subcortical feedback loops)
Diagnostic variance (dimensional vs categorical vs target symptom approach)
Syndromal variation (differing presentations over time)
Treatment limitations (limited empirical studies, nonrepresentative study samples)

Source: Reference 2

treatment-refractory OCD.[37] Although its exact mechanism of action is unclear, riluzole's effects are thought to be mediated via reduction in glutamatergic neurotransmission. IV ketamine has reported anti-OCD effects in a case report of a woman with treatment-resistant OCD. These effects occurred almost immediately and persisted for several days.[38]

Hallucinogens. Psilocybin, psilocin, and lysergic acid diethylamide have reported anti-OCD properties.[39] As schedule I substances, however, they are not available outside of sanctioned research protocols and may carry substantial risk. Nonetheless, their efficacy suggests that other compounds that share their mechanism of action—namely agonism of 5-HT2A and 5-HT2C receptors—may merit investigation as potential treatments for OCD.

Psychotherapy

Cognitive-behavioral therapy (CBT) has been shown to be effective for OCD as monotherapy and augmentation to pharmacotherapy. CBT consists of cognitive and behavioral components, typically involving some form of cognitive restructuring and exposure response prevention. Although these 2 types of interventions arise from independent traditions, in CBT they are frequently intertwined, particularly when the focus of OCD patients' anxiety is ego-dystonic thoughts.

One benefit of CBT over pharmacotherapy is that effects persist after treatment is terminated. A recent prospective study found CBT was effective for treatment-refractory OCD, with 74% of patients demonstrating clinical response after 20 to 25 sessions over 2 months and 61% maintaining clinical response 1 year after treatment.[40] CBT administered remotely via teleconference, also known as "teletherapy," has shown efficacy for OCD.[41]

Alternative medicine

Despite widespread use of herbal remedies for OCD, no trials have shown a strong positive effect. Both *Hypericum perforatum* (St. John's wort) and *Silybum marianum* (milk thistle) have been used to treat obsessive and compulsive symptoms; however, placebo-controlled trials did not find any significant differences in symptoms or side effects between treatment groups.[42,43] Lower-quality studies have reported modest effects for mindfulness meditation, yoga, and acupuncture.[44]

Because many patients continue to use complementary and alternative medicine therapies despite the lack of data on efficacy, it is important to monitor for potential

interactions with prescription medications. St. John's wort interacts with many medications because of induction of the cytochrome P450 (CYP) isoenzymes 3A4 and 2C9. This interaction may lower blood levels of alprazolam and clonazepam (3A4). Combining St. John's wort with SSRIs increases the risk of serotonin syndrome. Milk thistle inhibits CYP450 isoenzyme 3A4, and may increase serum levels of other medications metabolized by this pathway.

Invasive therapies

Invasive options may be considered after several pharmacotherapeutic and psychotherapeutic approaches have not been effective or when significant functional impairment remains (***Table 2, page 50***). These therapies typically are reserved for patients whose treatment resistance is strongest.

Electroconvulsive therapy (ECT). Although ECT is an effective tool for treatment-resistant mood disorders or treatment-resistant anxiety complicated by severe depression, studies have not found ECT to be effective for OCD. One uncontrolled case series reported considerable improvements in OCD patients the year after ECT, although improvement was correlated with improved depression scores.[45]

Vagal nerve stimulation (VNS). In an open-label study of 7 OCD patients who received VNS, 3 were acute responders—characterized by a ≥25% improvement on the Y-BOCS—and 2 received continued benefits at 4-year follow up (2 patients dropped out).[46]

Repetitive transcranial magnetic stimulation (rTMS). A meta-analysis of 3 RCTs of rTMS for patients with OCD did not yield a large or statistically significant effect.[47] Limitations of these trials included asymmetric stimulation sites (eg, left vs right only), limited stimulation sites (dorsolateral prefrontal cortex), different stimulation frequencies between studies, and a lack of sham stimulation conditions. A more recent RCT and subsequent review described moderate efficacy (defined by ≥25% decrease in Y-BOCS scores) compared with sham stimulations in OCD patients at 4 weeks, using the supplementary motor area as a stimulation site.[48,49]

The main limitation of rTMS is the inability to penetrate deeper brain structures implicated in OCD (eg, caudate nucleus, thalamus, anterior capsule fiber tracts), as well as a lack of specificity in stimulation site.

Surgical approaches. Cingulotomy is the most commonly employed surgical procedure for OCD in North America, likely because of a combination of clinical efficacy and low morbidity and mortality rates.[50] Of the >1,000 cingulotomies that have been performed at Massachusetts General Hospital, no deaths or postoperative infections have been reported and 2 subdural hematomas have occurred.[50] Common postsurgical side effects include transient headache, nausea, or difficulty urinating. The most serious common side effect—postoperative seizures—has been reported in 1% to 9% of cases.

Outcomes for these procedures cannot be fully assessed until at least 6 months to 2 years after the procedure, which suggests postoperative neural reorganization plays an important role in recovery. Direct comparisons of each lesion approach within studies are extremely rare. Overall, long-term outcomes of these approaches have demonstrated significant therapeutic effects of each of these procedures. Reported response rates vary between 30% to 70%, when applied to remission, response (≥35% Y-BOCS reduction), and functional improvements in quality of life.[50]

Deep brain stimulation (DBS). With this approach, small electrodes are inserted under precise stereotactic MRI guidance. The advantage of DBS over ablative surgery is the ability to adjust and customize neurostimulation. Following implantation, modifiable parameters of electrode stimulation include electrode polarity, intensity, frequency, and laterality. A specially trained psychiatrist can conduct parameter optimization during long-term follow-up.

continued

Clinical Point

Invasive therapies, such as surgery, ECT, VNS, rTMS, and DBS, typically are reserved for patients whose treatment resistance is strongest

Treatment-resistant OCD

Clinical Point

Outcomes for surgery for OCD cannot be fully assessed until 6 months to 2 years after the procedure

Table 2

Invasive therapies for treatment-resistant OCD

Therapy	Quality of evidence
Reversible	
Electroconvulsive therapy	Poor
Vagal nerve stimulation	Poor
Repetitive transcranial magnetic stimulation	Limited
Irreversible (surgical)	
Anterior capsulotomy. Target: anterior limb of the internal capsule	Fair
Anterior cingulotomy. Target: anterior cingulate and cingulum bundle	Fair
Subcaudate tractotomy. Target: substantia innominata, just inferior to the caudate nucleus	Fair
Limbic leucotomy. Target: anterior cingulotomy combined with subcaudate tractotomy	Fair
Deep brain stimulation. Multiple targets	Fair

OCD: obsessive-compulsive disorder

The first trial of DBS for OCD was reported in 1999 (N = 4), with the initial target selected based on the site of anterior capsulotomy. Three patients derived clinically observed benefit, although no validated questionnaires were administered.[51] Since then, at least 7 studies with blinded stimulation have been conducted, totaling 62 patients.[52]

In recent years, structures adjacent to the internal capsule also have been targeted based on the approach employed in ventral capsulotomy. Across all trials, response rates for this approach consistently have been in the 50% range, with average Y-BOCS score reductions ranging from 6.8 to 31 points.[53] Some patients have reported rapid improvements in anhedonia, and this approach is being employed in treatment-resistant depression.

Postoperative complications occur more often with DBS than with lesion approaches because of the prosthetic nature of the procedure (eg, increased risk of infection, lead malfunction, etc.). Additionally, batteries must be periodically explanted and replaced. Reported stimulation-related side effects include mood changes (transient sadness, anxiety, euphoria, and hypomania), sensory disturbances (olfactory, gustatory, and motor sensations), and cognitive changes (confusion and forgetfulness). These side effects typically are stimulation-dependent and disappear after altering stimulation parameters.

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continued

This month's instant poll

For 15 years, Mr. Z, age 67, has been treated for obsessive-compulsive disorder (OCD) with sertraline, 150 mg/d. Even with this medication, he still exhibits symptoms of the disorder, including compulsively washing his hands and a superstition about the number 6. **How would you address his treatment-resistant OCD?**

- ☐ Switch him to an antipsychotic, such as aripiprazole
- ☐ Prescribe an opioid, such as oral morphine
- ☐ Recommend cognitive-behavioral therapy
- ☐ Consider cingulotomy
- ☐ Increase sertraline to 250 mg/d

See **'Treatment-resistant OCD: Options beyond first-line medications'** *page 44-52*

Visit CurrentPsychiatry.com to answer the **Instant Poll** and see how your colleagues responded. ***Click on "Have more to say?"*** to comment.

SEPTEMBER POLL RESULTS

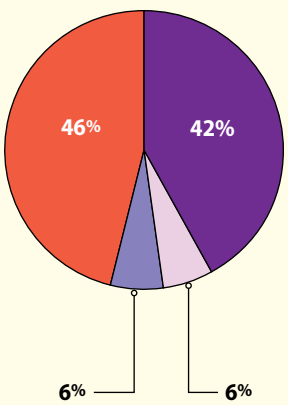
Mrs. T, age 28, has bipolar I disorder that is successfully treated with carbamazepine, 400 mg/d, and risperidone, 2 mg/d. On a recent visit, she tells you she is pregnant. **How would you counsel her?**

42% **Take a thorough history and review with Mrs. T the risks and benefits of medication exposure during pregnancy**

6% **Assess her preferences and beliefs regarding medication use during pregnancy and breast-feeding**

6% **Caution her against rapidly discontinuing her medications**

46% **Meet with Mrs. T, her family, and significant supports to discuss treatment options**



▲ Data obtained via CurrentPsychiatry.com, September 2011

SUGGESTED READING:
Vemuri M, Williams K. Current Psychiatry. 2011;10(9):58-66.

Treatment-resistant OCD

Clinical Point

The advantage of DBS over ablative surgery is the ability to adjust and customize neurostimulation

Related Resources

- American Psychiatric Association. Treatment of patients with obsessive-compulsive disorder. www.psychiatryonline.com/pracGuide/pracGuideTopic_10.aspx.
- Hyman BM, Pedrick C. The OCD workbook. Your guide to breaking free from obsessive compulsive disorder. 3rd ed. Oakland, CA: New Harbinger Publications Inc; 2010.
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Drug Brand Names

Alprazolam • Xanax
Aripiprazole • Abilify
Citalopram • Celexa
Clomipramine • Anafranil
Clonazepam • Klonopin
Dextroamphetamine • Adderall
Duloxetine • Cymbalta
Fluoxetine • Prozac
Fluvoxamine • Luvox
Haloperidol • Haldol
Ketamine • Ketalar
Memantine • Namenda
Methylphenidate • Ritalin
Morphine • MS Contin
Olanzapine • Zyprexa
Ondansetron • Zofran
Pindolol • Visken
Quetiapine • Seroquel
Riluzole • Rilutek
Risperidone • Risperdal
Sertraline • Zoloft
Tramadol • Ultram
Venlafaxine • Effexor
Ziprasidone • Geodon

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Bottom Line

Treatment resistance in obsessive-compulsive disorder can be defined as inadequate clinical response to several adequate treatment trials of selective serotonin reuptake inhibitors (SSRIs) or clomipramine. Evidence supports use of supratherapeutic doses of SSRIs, IV clomipramine, adjunctive antipsychotics, and cognitive-behavioral therapy. Invasive modalities have demonstrated efficacy but typically are reserved for patients whose treatment resistance is strongest.