A Qualitative Analysis of Nonresponse: Management of Treatment-Refractory Obsessive-Compulsive Disorder

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Serotonin reuptake inhibitors (SRIs), especially potent ones given at high doses over long periods of time, are often effective in the treatment of obsessive-compulsive disorder (OCD). However, a large percentage of patients do not respond to treatment with SRIs, and those who do respond often do not fully remit, which should be the standard goal of treatment in OCD. If a patient has been treated for several months and has not yet responded to treatment with several SRIs, the physician should perform a careful assessment of resistant and/or residual clinical symptoms and any comorbid conditions to determine which next-step treatment would be the most appropriate. One strategy for patients who have not responded to treatment with an SRI is to switch them to a serotonin-norepinephrine reuptake inhibitor, because some patients may respond better to agents that target multiple systems. Another promising approach is the augmentation of SRIs with neuroleptics. In addition, open trials have shown that intravenous (IV) clomipramine and IV citalopram may be effective in the treatment of resistant OCD. Novel pharmacotherapeutic treatments and electroconvulsive therapy have been attempted, with mixed success. Recently, researchers have been studying repetitive transcranial magnetic stimulation, vagal nerve stimulation, and neurosurgical approaches such as gamma knife capsulotomy and deep brain stimulation to learn if these procedures are effective in treating treatment-resistant OCD. Repetitive transcranial magnetic stimulation has possibilities not only as a therapy but also as an instrument that can help researchers describe the neurocircuitries involved in OCD. More results are needed before the effectiveness of the nonpharmacologic treatments for OCD can be determined.
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Obsessive-compulsive disorder (OCD) affects all spheres of functioning of those who have the disorder. Many individuals with OCD function at a much lower level than the general population. Treatment with serotonin reuptake inhibitors (SRIs) is effective in 40% to 60% of patients with OCD,[1] but that leaves a large percentage of patients who are nonresponsive to treatment. Poor outcome in OCD seems to be associated with a more severe and chronic course, which may occur in patients who do not respond to treatment. As an outgrowth to the International Obsessive-Compulsive Disorder Conferences, several research sites have been working together to collect data on treatment-refractory OCD.

The heterogeneous nature of the severely disabling condition of OCD creates a substantial challenge for the clinician, in that each therapeutic decision may take into account not only a quantitative evaluation of nonresponse but also a qualitative evaluation of nonresponse. Although several treatment guidelines have been proposed to overcome treatment-resistant OCD, decisions about next-step treatments are still deeply based on the clinical judgment of physicians. Even though subtypes of OCD[2,3] have not yet been validated in neurobiological studies utilizing genetics and neuroimaging, it is hypothesized that variations in the clinical dimensions of OCD may be due to different pathophysiologic substrates. Therefore, a careful assessment of resistant and/or residual clinical symptoms and any comorbid conditions[4] associated with the emergence of OCD or of OCD-spectrum disorders is necessary. When making a decision about whether to switch or augment medication as a next-step treatment, the physician should also take into consideration pharmacogenotype,[5] electrophysiologic measures, and functional brain imaging.[6] Prediction of treatment response based on pretreat-

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ment brain activity may become increasingly important in the future for understanding the mechanism of treatment response and nonresponse.

ADEQUATE TREATMENT TRIALS

Before declaring a patient's OCD to be treatment-refractory, the physician should make sure that the patient is truly nonresponsive to treatment and has not simply had an inadequate treatment trial. Higher doses of SRIs than those used in depression are frequently necessary to get a response in OCD. Potent selective serotonin reuptake inhibitors (SSRIs) like fluvoxamine at high doses over long periods of time seem to be the most effective in the treatment of this disorder. In a study of fluvoxamine for the treatment of OCD, Hollander et al.[7] started patients at a dose of 100 mg/day, rather than 50 mg/day, which was the initial dose in previous studies[8,9] with fluvoxamine. A more rapid onset of action in this study was reported compared with that in the previous studies. Fluvoxamine separated significantly from placebo at week 2 ($p < .050$) and continued to be significantly more effective than placebo throughout the trial. In a double-blind trial of paroxetine in the treatment of OCD,[10] patients enrolled in the study were initially given either paroxetine or placebo for 12 weeks. While the 20-mg/day dose did not separate from placebo, the 40-mg/day and 60-mg/day doses did. Results from these 2 studies support the use of higher doses of SSRIs in OCD than in depression.

The patients who completed the 12-week trial were given an additional 6 months of open maintenance treatment with paroxetine,[10] and they showed continued improvement on the Yale-Brown Obsessive Compulsive Scale (YBOCS). There may have been a differential dropout in that some of the people who did not respond well to paroxetine dropped out, but it can be seen from this study that maintenance treatment of patients who respond in the acute stage may not only prevent relapse but allow them continued improvement. At the end of the 6-month open-treatment period, the patients who responded to paroxetine were randomly assigned to blindly receive either paroxetine or placebo for another 6 months. The patients who received placebo were 2.7 times more likely to relapse than those who continued paroxetine. Long-term maintenance treatment is key in continuing improvement and preventing relapse, and an adequate dose and treatment duration are essential in determining whether a patient is truly resistant.

DEFINING RESPONSE TO TREATMENT AND REMISSION OF OCD

Remission has become the standard goal for clinical outcome in studies of depression and the anxiety disorders, but it has not been addressed in OCD. In treating OCD, researchers and clinicians should not only aim for a certain level of change from baseline but also seek a standard final result. To do this, the criteria describing response to treatment of OCD need to be consistent, but so far, there is a lack of consensus.

At the sixth International Obsessive-Compulsive Disorder Conference, one author (E.H.) proposed that remission be defined either as a YBOCS score of ≤ 16, because a patient at that degree of severity would not be entered into clinical trials, or as a YBOCS score ≤ 8, because at that level a patient's symptoms are not severe enough to meet the criteria for a diagnosis of OCD. Another author (W.K.G.) suggested defining remission as a total YBOCS score ≤ 10, specifically with item 1 and item 6 not greater than 1. A score of 1 on those items means that the symptoms of OCD take up less than an hour of the patient's time each day, which is below the threshold for a diagnosis of OCD.

Pallanti et al.[1] reviewed several controlled trials of medication treatment in OCD and found a lack of standardized operational criteria by which to characterize patients' response to treatment. Also, many patients are considered treatment refractory after they have failed 1 trial of an SRI alone, even though other treatments may be the most effective treatment for the patient's particular subtype of OCD. This review proposed categorizing treatment response into 10 levels in which level 1 denotes nonresponse to 1 SSRI alone or cognitive-behavioral therapy (CBT) alone, and level 10 denotes nonresponse to at least 3 SRIs, CBT, psychoeducation, other classes of antidepressants such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), and neurosurgery.

As a general rule, response could be classified as a rating of much or very much improved on the Clinical Global Impressions scale (CGI) and a $\geq 35\%$ reduction in YBOCS score from baseline. Partial response could be classified as a $< 35\%$ reduction in YBOCS score. *Treatment resistance* could be defined as having failed 1 adequate trial of an SRI, and *treatment refractory* as having failed at least 2 adequate SRI trials with no response at all to treatment.

NEW PHARMACOLOGIC TREATMENT OPTIONS FOR REFRACTORY PATIENTS

Once it has been determined that a patient is truly treatment-refractory, the physician must decide on the best next-step strategy for treatment. Although SRIs and CBT have been successfully used in the treatment of resistant OCD,[11] alternative treatments are emerging for treatment-refractory patients.

Serotonin-Norepinephrine Reuptake Inhibitors

One strategy for patients who have not responded to treatment with an SRI is to switch them to a serotonin-

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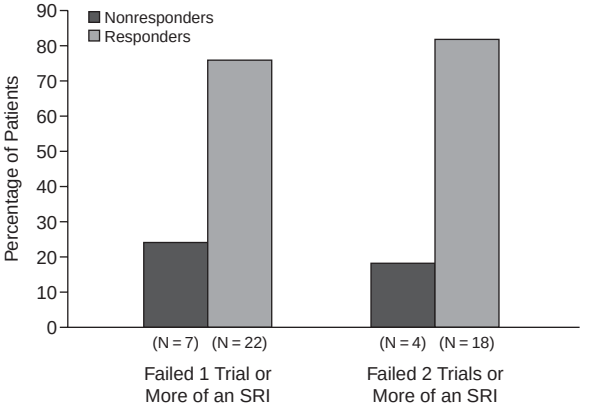
norepinephrine reuptake inhibitor (SNRI) because some patients may respond better to agents that target multiple systems. To date, the majority of data on the use of SNRIs in the treatment of OCD comes from trials with venlafaxine. In a study by Ravizza et al.[12] (see Hollander et al.[11] for a description of the study), 28 patients who failed 2 adequate trials of an SSRI were switched to the SNRI venlafaxine (N = 8), the TCA (and SRI) clomipramine in high doses (150–225 mg/day, N = 11), or to the SSRI citalopram (N = 9). Response was defined as at least a 35% improvement in YBOCS score and a CGI score ≤ 2. Of the patients who completed the trial, 3 (42.8%) of the 7 patients taking venlafaxine responded, 3 (37.5%) of the 8 patients taking clomipramine responded, and 1 (14.3%) of the 7 patients taking citalopram responded. These results suggest that if the physician switches the patient from one medication to another that has a different mechanism of action, there may be a preferential treatment response, especially in SSRI nonresponders.

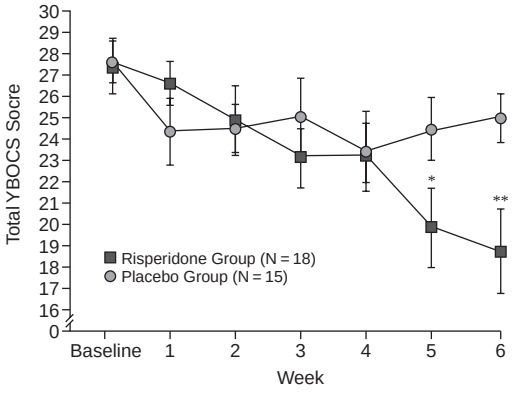
Hollander et al.[13] studied the efficacy of venlafaxine in patients who were resistant to prior treatment with SRIs. Patients were treated with a relatively high dose (37.5–375 mg/day, mean = 232.2 mg/day) of venlafaxine. Response was defined as a CGI-Improvement score of 1 to 2 (very much to much improved). Of the 29 patients who had previously not responded to 1 or more trials of an SRI, 22 (75.9%) responded to treatment with venlafaxine (Figure 1). Of the 22 patients who had not responded to 2 or more trials of an SRI, 18 (81.8%) responded to treatment with venlafaxine (see Figure 1). However, this trial was not placebo controlled; a prospective, double-blind, placebo-controlled trial is necessary to confirm these encouraging findings.

Figure 1. Response to Venlafaxine in Patients Previously Nonresponsive to Serotonin Reuptake Inhibitors (SRIs)[a]



[a]Data from Hollander et al.[13]

Figure 2. Change in Mean Yale-Brown Obsessive-Compulsive Scale (YBOCS) Scores in Patients With Obsessive-Compulsive Disorder Given Risperidone or Placebo in Addition to a Serotonin Reuptake Inhibitor[a]



[a]Reprinted with permission from McDougle et al.[14]
*p = .01.
**p = .005.

Atypical Antipsychotics

The most promising approach to date in the treatment of patients with refractory OCD has been the addition of neuroleptics to SRIs. McDougle et al.[14] studied the use of risperidone in patients who had been refractory to treatment with SRIs. Thirty-six patients were randomly assigned to receive 6 weeks of risperidone treatment (N = 20) or placebo (N = 16) in addition to an SRI. Risperidone separated significantly from placebo at week 5 and continued its separation through week 6 (Figure 2). Nine (50%) of the 18 patients treated with risperidone responded, while none of the 15 patients given the placebo responded. Fourteen patients given a placebo during the double-blind phase of the study received open-label risperidone after its end; 7 (50%) of these patients responded to treatment.

An earlier study[15] suggested that comorbid tic disorder might serve as a clinical marker for employing neuroleptics in addition to fluvoxamine. However, in the 2000 study,[14] patients with comorbid tics and patients without tics seemed to respond at an equal rate.

Shapira et al.[16] recently completed a study sponsored by the National Institute of Mental Health that studied the addition of olanzapine to fluoxetine in treatment-refractory OCD. Patients who had not responded to 8 weeks of open-label treatment with fluoxetine were randomly assigned to receive either olanzapine (N = 22) or a placebo (N = 22) in addition to fluoxetine for 6 weeks. Both the group that was given olanzapine in addition to fluoxetine and the group that continued to take fluoxetine alone improved significantly over the additional 6 weeks of treatment. Although there was a numerical advantage to the group that was given olanzapine plus fluoxetine, no statistically significant difference in improvement between the 2 groups was reported. The explanation for the lack of separation for the 2 groups seems to

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be that patients may continue to benefit when SRI treatment is continued past 6 weeks. Physicians should probably wait longer than 8 weeks, possibly 12 to 14 weeks, before augmenting an SRI with an antipsychotic. The patient may simply improve with time by taking the SRI alone.

Intravenous Medications

Intravenous (IV) clomipramine has been effective in the treatment of OCD in open trials. Koran et al.[17] administered IV clomipramine to 5 patients with severe OCD (YBOCS score of 25 or more), 4 of whom had previously been refractory to treatment. The patients were given IV clomipramine 6 days per week for 6 to 7 weeks, with a starting dose of 25 mg and a mean daily dose of 140 mg at week 4. At the end of treatment, patients' YBOCS scores decreased a mean of 71% from baseline. All patients responded to treatment, with a minimum decrease in YBOCS score of 26% from baseline.

Intravenous citalopram has also been tested specifically in treatment-refractory OCD. Pallanti et al.[18] tested IV citalopram in 39 patients who had failed at least 2 adequate trials of an SRI. The starting dose of 20 mg/day was titrated to 40 to 80 mg/day during the 21-day trial. Of the 38 patients who completed the trial, 27 (71%) responded, defined as a ≥ 20% decrease in YBOCS scores from baseline. The mean YBOCS score decreased from 30.2 at baseline to 22.5 at endpoint, a 25% decline.

Novel Pharmacotherapeutic Treatments

A wide range of medications such as MAOIs, anticonvulsants, and opiate agents have been attempted in treatment-refractory OCD with varying results.[11] Glutamate has been found to possibly play a role in OCD. Activation in the orbital frontal cortex may be passed on to the striatum by glutamatergic innervation. Inhibition of glutamatergic innervation may reduce obsessive-compulsive symptoms. A study of an N-gluar-2 agonist, which acts on the autoreceptor to inhibit a phasic release of glutamine, is currently underway.

There is also growing evidence that serotonin-1D ($5\text{-}HT_{1D}$) plays a role in the symptoms of OCD.[19] Compounds are currently under development that make use of the $5\text{-}HT_{1D}$ hypothesis in their mechanism of action for OCD.

NONPHARMACOLOGIC TREATMENTS FOR TREATMENT-REFRACTORY OCD

When patients have had many trials of medication and have shown no response, other strategies may be necessary. Electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagal nerve stimulation (VNS), and, recently, neurosurgical approaches, particularly gamma knife capsulotomy and deep brain stimulation (DBS), have been attempted for treatment-refractory OCD.

Electroconvulsive Therapy

ECT, which has been used successfully in other psychiatric disorders such as depression, has shown little efficacy in OCD. There have been some reports of its usefulness in depressed patients with OCD, but it does not seem to have much effect on obsessional symptoms.[11]

Repetitive Transcranial Magnetic Stimulation

Repetitive TMS, primarily used for the treatment of depression, has also been tested in patients with treatment-refractory OCD.[20] There has been some indication that compulsive urges are reduced by rTMS. A study by Greenberg et al.[21] found that right lateral prefrontal rTMS reduced compulsive symptoms significantly for up to 8 hours after administration. Obsessive symptoms were not significantly reduced. However, rTMS may help researchers describe the neurocircuitries involved in treatment-resistant OCD. More research is needed on rTMS in OCD.

Vagal Nerve Stimulation

VNS has also mainly been used in the treatment of depression, but it has been tested as a treatment for OCD as well. Results in patients so far have been mixed,[11] but more research is needed.

Gamma Capsulotomy

Another treatment being investigated for treatment-refractory OCD is gamma capsulotomy. The gamma knife is cobalt-60, which is a source of radiation. Gamma knife surgery is ablative, but the surgeon does not have to perform a craniotomy. In a study by Rasmussen[22] (see Hollander et al.[11] for a description of the study), 38% to 50% of patients who received bilateral double lesions showed clinical improvement. More research on gamma capsulotomy is currently underway.

Deep Brain Stimulation

DBS is approved for the treatment of essential tremor and for Parkinson's disease, and it appears that it may be effective in the treatment of OCD as well. Researchers in Belgium[23] studied the efficacy of DBS in 4 patients who had been refractory to at least 2 or 3 adequate trials of SSRIs, clomipramine, antipsychotic augmentation strategies, and CBT. Three of the 4 patients experienced at least a 35% drop in YBOCS score after the DBS.

DBS is not ablative like a capsulotomy, but it is an invasive procedure. A craniotomy is performed with the patient awake. The wires are tunneled under the skin and the electrodes are implanted in the internal capsule. Like other invasive procedures, the significant risks—hemorrhage, seizures, and infection—are during the implantation stage. After the craniotomy is performed, the

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physician can test the stimulation with the patient awake to see if there are behavioral effects.

The notion of reversibility is appealing in that if the procedure does not work, the surgeon should be able to pull out the wires and the stimulators and return the patient to his or her original mental state before the surgery was performed. From postmortem data, there is some evidence of gliosis around the contact points, but no other significant changes. A possible benefit of DBS is adjustability. After the procedure has been performed, the voltage, frequency, and pulse width can be changed, and the location and configuration of the stimulation can be varied.

CONCLUSION

Although SRIs are effective in the treatment of OCD in many patients, some patients will be refractory to treatment. Remission, not just response, should be the goal of treatment. Before deciding that a patient is treatment-refractory, physicians should determine whether the SRI trial has been adequate. Doses of SSRIs higher than the ones given for depression are often necessary to effectively treat OCD, and it also may take longer for the patient to show a response. If the patient is truly nonresponsive to SRIs, physicians should consider switching the patient to an SNRI, which acts on multiple receptors. Atypical antipsychotics and IV citalopram and clomipramine have also been found to be effective in the treatment of treatment-refractory OCD. Other treatments for treatment-refractory OCD are in development. Novel pharmacotherapies, based on the glutamate and 5-HT_{1D} hypotheses, and nonpharmacotherapeutic treatments such as rTMS, VNS, gamma knife capsulotomy, and DBS are currently being studied for treatment-refractory OCD.

Drug names: citalopram (Celexa), clomipramine (Anafranil and others), fluoxetine (Prozac and others), olanzapine (Zyprexa), paroxetine (Paxil and others), risperidone (Risperdal), venlafaxine (Effexor).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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