Pharmacotherapy for Obsessive-Compulsive Disorder

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Pharmacotherapeutic options for obsessive-compulsive disorder (OCD) have expanded over the past half-century since medications were first found to be effective for the treatment of OCD. Currently, the serotonin reuptake inhibitors (SRIs) represent the first-line pharmacotherapy for OCD. High dosages and long trials of the SRIs are needed for adequate treatment of OCD. The use of SRIs for the treatment of OCD is reviewed, then other pharmacotherapeutic treatment options, including SRI augmentation and alternative monotherapies, are discussed. The preponderance of data demonstrates that SRI augmentation with neuroleptics is efficacious for treatment-refractory OCD. There is substantially less evidence supporting other alternative strategies. Finally, neurosurgical and device-based approaches for treatment-refractory OCD are reviewed. © 2004 Wiley Periodicals, Inc. J Clin Psychol/In Session 60: 1195–1202, 2004.

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Obsessive-compulsive disorder (OCD) has a lifetime prevalence of approximately 2–3%. Although the pathophysiological characteristics of OCD are not completely understood, converging evidence suggests that dysfunction of corticostriatal circuits plays a central neurobiological role in OCD. Specifically, both structural and functional abnormalities have been demonstrated in the orbitofrontal cortex and the caudate, a territory of the striatum, in patients who have OCD. These abnormalities appear to be specific to OCD and may account for some of the unique phenomena associated with the treatment of OCD. Moreover, functional neuroimaging abnormalities in patients who have OCD appear to become attenuated after successful pharmacotherapy or behavioral therapy. Finally,

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studies have suggested that abnormalities in serotonergic and dopaminergic neurotransmission are associated with OCD.

Until relatively recently, effective treatments for OCD were lacking. In the late 1960s, the first clinical trial to demonstrate that clomipramine (Anafranil) was an effective treatment for OCD was published. Since then, a large body of literature on the pharmacotherapy of OCD has emerged and treatment options have grown tremendously. The goals of this practice-friendly review are to provide an up-to-date account of this literature and to outline state-of-the-art pharmacological approaches to treating OCD.

General Considerations in the Treatment of OCD

The importance of correctly diagnosing OCD cannot be overstated. Although a thorough clinical evaluation should yield a correct diagnosis most of the time, consideration of a differential diagnosis is crucial. For example, the obsessions associated with OCD may be confused with the ruminations associated with depression, the racing thoughts of mania, or psychotic symptoms. Comorbid diagnoses in addition to OCD may also be present, and such comorbid conditions may influence optimal selection of treatments. Major depressive disorder, other anxiety disorders, and substance abuse are the comorbid diagnoses most frequently encountered in patients who have OCD. Concurrent treatment of these comorbid disorders is also imperative. Although symptoms associated with these comorbid diagnoses may improve with successful treatment of OCD, if left untreated they may interfere with the treatment of OCD. Serotonin reuptake inhibitors (SRIs) are the first-line treatment for OCD and for many of these comorbid diagnoses.

Another important consideration in the treatment of OCD is the definition of response. The majority of pharmacotherapy trials for OCD have used a reduction of 25–35% of Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores from baseline as the response criterion. Therefore, many patients who are characterized as responders often still have significant residual symptoms. Nevertheless, a 50% reduction, for example, from a baseline Y-BOCS score is usually associated with substantial functional improvement. Nonetheless, it is best to inform patients at the outset of treatment that 100% improvement is rare; 25–50% symptom reduction is the norm.

Finally, although this article focuses on pharmacotherapy for OCD, most experts consider various forms of exposure and response prevention therapy an integral part of treatment for OCD. After being presented with the treatment options for OCD, some patients may choose exposure and response prevention alone or pharmacotherapy alone. The results of studies examining the efficacy of the combination of pharmacotherapy and exposure and response prevention are mixed. However, the combination of exposure and response prevention and pharmacotherapy is certainly warranted in patients who have not responded to either treatment alone.

First-Line Pharmacotherapy for OCD

First-line pharmacotherapy treatments for OCD are the serotonin reuptake inhibitors (SRIs). The SRIs include all of the selective serotonin reuptake inhibitors (SSRIs) (fluoxetine [Prozac], sertraline [Zoloft], paroxetine [Paxil], fluvoxamine [Luvox], citalopram [Cela- exa], and escitalopram [Lexapro]), as well as clomipramine, a tricyclic antidepressant with a mechanism of action that primarily involves serotonin reuptake inhibition. The efficacy of the SRIs for the treatment of OCD has been established for decades. A large, growing number of randomized, double-blind, placebo-controlled trials have demonstrated the efficacy of the SRIs for the treatment of OCD (for reviews see Cartwright &
Hollander, 1998; Dougherty & Rauch, 1997; Dougherty, Rauch, & Jenike, 2002; Greist, Jefferson, Kobak, Katzennick, & Serlin, 1995; Jenike 1998). Although the degree of response has varied among studies, most studies have found that 40–60% of patients respond to the SRIs, with a 20–40% mean decrease in OCD symptoms (Greist et al., 1995). Although fewer controlled comparative trials of the SRIs for the treatment of OCD have been conducted, it does not appear that any SRI is more efficacious than another SRI for the treatment of OCD. However, controlled head-to-head trials of SRIs and tricyclic antidepressants in the treatment of OCD have demonstrated that SRIs are more efficacious than tricyclic antidepressants (other than clomipramine) and that tricyclic antidepressants are no more efficacious than placebo.

Although SRIs are used to treat a number of psychiatric disorders, there are differences in the ways the SRIs are used for the treatment of OCD. One major difference is dosage. Studies have shown that higher dosages of SRIs than are typically used to treat other disorders, such as major depression, are usually required to achieve response in OCD. Standard recommended dosages of the SRIs for the treatment of OCD (see Table 1) are 80 mg/day of fluoxetine, 200 mg/day of sertraline, 60 mg/day of paroxetine, 300 mg/day of fluvoxamine, 60 mg/day of citalopram, 20–30 mg/day of escitalopram, and 250 mg/day of clomipramine. Of course, some patients respond to lower SRI dosages.

A second major difference between the use of SRIs in the treatment of OCD as compared to treatment of other disorders is the latency period from initiating a trial to the time of response. Whereas patients who have major depression treated by SRIs usually respond within 2–6 weeks, response may not occur in OCD patients for 10–12 weeks. For this reason, most practitioners escalate the dosage of SRIs relatively quickly so that the required 10- to 12-week trial period may begin. The alternative approach, a 10- to 12-week trial after each dosage escalation (e.g., fluoxetine 20 mg/day, 40 mg/day, 60 mg/day, and, finally, 80 mg/day), could require as much as a year. If, after response, a lower dosage is desired (e.g., because of side effects), the dosage can be lowered to determine whether the side effects dissipate and response is maintained. Although it is not clear why a longer trial with SRIs is necessary for the treatment of OCD, animal studies have found that changes in intermediate gene expression during exposure to SRIs in the orbitofrontal cortex do not occur for 8–12 weeks. In summary, during the initial dosage escalation it is recommended to target a high therapeutic dosage with the up-titration limited principally by side effects. Once a satisfactory therapeutic response has been achieved, some tapering of the dosage is possible to determine the lowest effective dosage for the individual patient.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Length of Treatment</th>
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<tbody>
<tr>
<td>Clomipramine</td>
<td>Up to 250 mg/day</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Up to 80 mg/day</td>
<td>12 weeks</td>
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<tr>
<td>Sertraline</td>
<td>Up to 200 mg/day</td>
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<tr>
<td>Fluvoxamine</td>
<td>Up to 300 mg/day</td>
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<td>Paroxetine</td>
<td>Up to 60 mg/day</td>
<td>12 weeks</td>
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<tr>
<td>Citalopram</td>
<td>Up to 60 mg/day</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Up to 20–30 mg/day</td>
<td>12 weeks</td>
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Patients often inquire about the recommended length of treatment by SRIs. Unfortunately, OCD is a chronic disorder that often requires chronic treatment. Few medication discontinuation trials have been conducted in OCD patients; the majority, but not all, found very high relapse rates after SRI discontinuation. Some studies have suggested that lower SRI dosages can be used for maintenance treatment, but further study of this possibility is needed. Lastly, many experts believe that including exposure and response prevention in treatment may lessen the chance of relapse after medication discontinuation. We often cite the possibility of relapse as a reason for using exposure and response prevention in conjunction with pharmacotherapy when discussing treatment options with patients.

Other Pharmacotherapy Approaches to OCD

If patients do not respond to treatment with SRIs as monotherapy, two pharmacotherapy options entail SRI augmentation or alternative monotherapies. Because the existing data provide stronger evidence for the efficacy of SRI augmentation, we recommend utilizing this strategy before initiating alternative monotherapies. SRI augmentation is also an effective strategy for OCD patients who have experienced partial response to SRI monotherapy.

SRI Augmentation

**Neuroleptics.** The striatum is also implicated in the pathophysiology of OCD; therefore, agents that exert their effects on the striatum may be efficacious in its treatment. Clinical trials of neuroleptic augmentation of the SRIs have provided the strongest data supporting efficacy in the treatment of OCD. Although conventional neuroleptics have long been used for SRI augmentation, only one controlled study has demonstrated the efficacy of this method (McDougle, Goodman, Leckman, Lee, Heninger, & Price, 1994). This study suggested that OCD patients who have comorbid tics were more likely to respond to SRI augmentation with haloperidol (Haldol) than OCD patients who did not have comorbid tics. However, more recent studies have revealed that atypical neuroleptics are effective SRI augmentation agents for OCD patients who and who do not have comorbid tics (McDougle, Epperson, Pelton, Wasylink, & Price, 2000). Although one controlled study (McDougle et al., 2000) has demonstrated the efficacy of SRI augmentation with risperidone (Risperdal), a growing number of uncontrolled studies suggest that other atypical neuroleptics may be useful SRI augmentation agents as well. Typically dosages at the lower end of the range recommended for the treatment of psychosis are adequate for SRI augmentation in OCD patients. For example, the controlled study by McDougle and associates (2000) cited above used doses of 1–4 mg/day of risperidone for SRI augmentation. An advantage of SRI augmentation with neuroleptics over initiation of a trial with another monotherapeutic agent is that only a 4-week trial is needed for augmentation, whereas another 10- to 12-week trial would be necessary for the monotherapy trial. Finally, it is important to note that use of atypical neuroleptics may be a useful treatment strategy when they are employed in combination with SRIs, but there are numerous reports of atypical neuroleptics’ inducing or worsening obsessive-compulsive symptoms when used without an SRI and, perhaps especially, when used at higher antipsychotic dosages (for review, see Lykouras, Alevizos, Michalopoulo, & Rabavilas, 2003).

**Clomipramine.** Another strategy commonly used by experts, despite little empirical support for it, is the combination of an SSRI and clomipramine. One open-label trial of
the combination of citalopram and clomipramine in patients who had SRI-refractory OCD found that this combination was more effective than citalopram alone. Clinicians utilizing this approach must be cognizant of the interactions between clomipramine and SSRIs, which result in an increased risk of toxicity.

Other agents. Clinical trials of SRI augmentation involving other agents have been less encouraging. Although case series and uncontrolled trials have suggested that buspirone (BuSpar) augmentation may be effective, two controlled trials have not demonstrated efficacy of buspirone augmentation of SRIs in the treatment of OCD. One controlled trial found clonazepam an effective augmenting agent. Likewise, although case reports suggested that lithium may be effective as an augmenting agent, the only two controlled trials of lithium augmentation of SRIs for the treatment of OCD have not demonstrated efficacy. One clinical trial found that adding pindolol to an SRI resulted in a significant improvement in OCD symptoms. Two clinical trials of SRI augmentation with inositol did not demonstrate efficacy.

Alternative Monotherapies

It might be expected that other agents that influence the serotoninergic and dopaminergic systems may be useful in the treatment of OCD, but data from clinical trials of alternative monotherapies for the treatment of OCD have not unequivocally shown that any of these agents is efficacious. These trials have primarily focused on other antidepressants, anxiolytics, and other experimental agents (for review, see Hewlett, 1997).

Other antidepressants. One double-blind placebo-controlled study of venlafaxine (Effexor), a dual serotoninergic and noradrenergic reuptake inhibitor, demonstrated no significant clinical improvement; venlafaxine was no more effective than placebo. However, another double-blind, head-to-head study comparing venlafaxine to paroxetine found that the two agents were equally efficacious; the response rates were approximately 40% for each treatment group. Other evidence supporting the efficacy of venlafaxine for the treatment of OCD includes small open-label studies and case reports. Three of four controlled trials of monoamine oxidase inhibitors, which block the degradation of serotonin and dopamine, for the treatment of OCD have not demonstrated efficacy. However, one of these studies suggested that a subgroup of patients who have symmetry obsessions did respond to phenelzine (Nardil). One controlled trial found that phenelzine and clomipramine were both effective treatments for OCD and that there was no significant difference in efficacy when comparing the two agents.

Anxiolytics. One controlled trial of buspirone, a 5-HT1A (serotonin 1A receptor) partial agonist, versus clomipramine found them equally efficacious; the response rate for both agents was greater than 55%. Two controlled trials of clonazepam (Klonopin) for the treatment of OCD have been conducted. One placebo-controlled study of clonazepam versus clomipramine versus clonidine found that clonazepam and clomipramine demonstrated comparable efficacy, and both demonstrated superiority to placebo. Another study failed to demonstrate no difference between clonazepam and placebo.

Other Experimental Agents. Clinical trials have been performed with other experimental agents; these show varying degrees of promise. For example, one controlled study of inositol, a precursor for the second messenger phosphatidyl-inositol system, in the
treatment of OCD demonstrated efficacy. Also, reports have suggested that novel treatments such as antiandrogens and opioids may provide effective treatment. The rationale for the use of antiandrogens in the treatment of OCD is based on reports of some OCD patients who noted an improvement of their OCD symptoms while being treated with gonadal hormones for other medical conditions. Studies of opioids for the treatment of OCD are based on the knowledge that some opioid agents such as tramadol not only bind to opioid receptors, but also inhibit serotonergic and noradrenergic reuptake.

Neurosurgical and Device-Based Approaches

**Neurosurgical Approaches**

For OCD patients for whom multiple trials of medication and exposure and response prevention have failed, neurosurgery may be a viable option. Neurosurgical procedures utilized for treatment-refractory OCD include anterior cingulotomy, limbic leukotomy, and anterior capsulotomy. The mechanism of action of these procedures is unknown; the hypothesis is that the lesions produced by surgery disrupt dysfunctional circuitry associated with OCD. Prospective trials of anterior cingulotomy and anterior capsulotomy have demonstrated response rates as high as 45% (Dougherty et al., 2002; see Cosgrove & Rauch, 2003; Greenberg et al., 2003 for reviews). In order for patients to be eligible for these procedures, most or all other available treatments must have failed. Thus, these response rates are quite clinically significant. However, it has been difficult to conduct controlled studies of these procedures as sham procedures that require craniotomy are not ethical. Newer surgical techniques that do not require craniotomy (e.g., by gamma knife) may allow for more controlled studies.

**Device-Based Approaches**

There are no controlled data regarding the efficacy of electroconvulsive therapy (ECT) for OCD. Although utilizing ECT to treat comorbid affective illness may be warranted, there is little to support the use of ECT for obsessive-compulsive symptoms. Transcranial magnetic stimulation (TMS) is a technique currently being studied primarily for the treatment of affective disorders. This technology uses a magnetic field to alter neurotransmission in focal areas of cortex and can be applied to target frontal regions implicated in the pathophysiology of OCD. Some preliminary data suggest that TMS, administered to lateral prefrontal regions, may provide effective treatment for OCD (Greenberg et al., 1997); further studies are needed.

**Combined Neurosurgical/Device-Based Approaches**

Deep brain stimulation (DBS) utilizes electrodes implanted in specific targets within the brain and then turned on either to chronically stimulate or to inhibit surrounding brain tissue. DBS has been used to treat neurological illnesses such as Parkinson’s disease. Studies of use of DBS in brain regions associated with the pathophysiology of OCD for treatment-refractory OCD are currently underway; preliminary results are encouraging (Gabriels, Cosyns, Nuttin, Demeulemeester, & Gymbels, 2003).

**Case Illustration**

William is a 26-year-old single white man who had symptoms consistent with OCD that began when he was approximately age 20. He first sought treatment for his OCD symptoms
4 years ago. He has participated in exposure and response prevention since then and shown some decrease in his symptoms. However, he continues to fear that he becomes contaminated whenever he touches surfaces that he perceives as “dirty.” These may include doorknobs, toilets, and even other people. He avoids “dirty” places and things and when he is exposed to surfaces that he feels are contaminated, he often washes his hands for as long as 1 hour. William has no comorbid diagnoses. He was treated for a few months 3 years ago with clomipramine with no relief of his symptoms. He has not used any other medications for OCD symptoms in the past. His therapist recommended that he have a psychopharmacological evaluation.

After a thorough psychopharmacological evaluation, the psychiatrist recommended treatment with an SSRI while William continued exposure and response prevention. William began to use fluoxetine, with a gradual increase in the dosage to 80 mg per day. After a 12-week trial with fluoxetine, William noticed no change in his OCD symptoms. The psychiatrist then discontinued the fluoxetine and began treatment with escitalopram. William noticed no change in symptoms for 8 weeks and began to feel discouraged. However, over the subsequent 4 weeks William noticed a gradual decrease in OCD symptoms. He still had a strong urge to wash his hands when he felt contaminated but was sometimes able to resist washing or shorten the duration of time that he spent washing. He and his treating psychiatrist estimated that his symptoms had decreased approximately 20%.

Because treatment with two SRIs failed and because William had a partial response to a third, the psychiatrist elected to augment the escitalopram rather than initiate a trial with another SSRI. William agreed to begin risperidone 0.5 mg twice a day. After 1 week, the dosage was increased to 1 mg twice a day. Over the next 2 weeks, William noticed further improvement of OCD symptoms. William and his psychiatrist estimated that his OCD symptoms had now improved by as much as 50%. Other than some mild sedation associated with the initiation of risperidone that gradually subsided, William experienced no side effects of the medications. He continued to take the medication and participate in exposure and response prevention. William found exposure and response prevention much easier than it was before he started the medications.

Clinical Issues and Summary

In addition to cognitive-behavioral interventions, SRIs are the first-line pharmacological treatment option for OCD. It is especially important that relatively high dosages of SRI be used to treat OCD. In addition, long trial durations (10–12 weeks) are required. It is important to inform patients that they may not notice an improvement of OCD symptoms for 10–12 weeks so that they do not become discouraged. Although most patients experience at least a partial response after treatment with an SRI, some SRI nonresponders or partial responders may benefit from either SRI augmentation or alternative monotherapies. Data supporting the efficacy of SRI augmentation with neuroleptics are stronger than data for efficacy of other augmentation strategies or alternative monotherapies. However, strategies that involve alternative monotherapies or SRI augmentation with agents other than neuroleptics may be useful for patients who do not respond to SRI monotherapy or SRI augmentation with a neuroleptic. Finally, neurosurgical and device-based therapies may offer a viable option for severe treatment-refractory OCD patients.

Select References/Recommended Readings


