Biological, Pharmacological, and Somatic Treatments for Obsessive-Compulsive Disorder

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For many patients, obsessive-compulsive disorder is a lifelong illness extending from early childhood into adulthood. However, pharmacological and behavioral treatments at adequate doses and duration offer a majority of patients improvement in symptoms and functioning. At the present time, there are a number of effective medications with relatively tolerable side effects. Experimental biological treatments for the truly treatment refractory, such as neurosurgery, deep brain stimulation, and vagal nerve stimulation, are being developed and refined, and may ultimately offer new hope to patients who do not respond to traditional treatments. [Brief Treatment and Crisis Intervention 3:275–290 (2003)]

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A growing understanding of the pathophysiology of obsessive-compulsive disorders (OCDs) has been helpful in stimulating the development of biologic treatments. Neuroimaging studies and research on neuroreceptors implicate serotonin and certain brain circuits in OCD’s pathogenesis. The purpose of this article is to review some of the theoretical underpinnings of biological treatments and to present evidence for the efficacy of these treatments in OCD.

Biological Mechanisms in OCD

Neuroanatomical and Neuroimaging Considerations

An increasing number of studies have been done with structural and functional neuroimaging. Structural imaging uses computerized tomography (CT) and magnetic resonance imaging (MRI) (Robinson et al., 1995; Szefszko et al., 1999); functional imaging uses positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS). These studies have shown abnormalities in patients with OCD at rest and with symptom provocation paradigms (Breiter et al., 1996; Cottraux & Gerard, 1998; Rauch et al., 1994; Saxena, Brody,
Schwartz, & Baxter, 1998). Some studies have even shown a “normalization” of brain functioning following successful pharmacotherapy and cognitive-behavioral therapy (CBT) (Baxter et al., 1992a; Benkelfat et al., 1990; Hoehn-Saric, Pearlson, Harris, Machlin, & Camargo, 1991; Swedo et al., 1992).

The majority of these studies have implicated abnormalities in the orbitofrontal cortex, anterior cingulate cortex, and structures of the basal ganglia (especially the caudate nucleus) and thalamus. These structures were originally proposed to be linked in a neuroanatomical circuit by Insel (1992) and Baxter (1992b). More elaborated models by Saxena and colleagues (1998) and Blier and de Montigny (1999) propose a complicated balance, involving the neurotransmitter serotonin, within a three-way circuit between the orbitofrontal cortex, head of the caudate nucleus, and the thalamus (Baxter et al., 1987, 1988, 1992b; Blier & de Montigny, 1999; Nordahl et al., 1989; Saxena, Brody, Schwartz, & Baxter, 1998; Swedo et al., 1989). Successful treatment with various pharmacological agents (clomipramine, fluoxetine, and paroxetine) and with CBT has been shown to result in a decrease in glucose metabolism in the caudate nucleus (indicating change in the activity of this circuit) (Saxena et al., 1998).

**Neurochemical Considerations**

There are also several lines of evidence from a neurochemical perspective that support a role for the neurotransmitter serotonin in OCD. The hypothesis that OCD involves an abnormality in serotonin transmission has been called the serotonin hypothesis. Data supporting this hypothesis come from several different sources. First, agents that effectively treat OCD affect serotonin (the serotonin reuptake inhibitors [SRIs]), with a specific action on the presynaptic reuptake of serotonin into the serotonin-releasing neuron (Greist, Jefferson, Kobak, Katzelnick, & Serlin, 1995a). While the exact mechanism of action of the SRIs is unclear, it appears that serotonin reuptake is followed by a cascade of changes both presynaptically and postsynaptically (Blier & de Montigny, 1999). A role for serotonin is also supported by studies measuring neurotransmitter or metabolite concentration in the central and peripheral nervous systems, as well as pharmacological challenge paradigms that measure behavioral and neuroendocrine effects produced by acute administration of pharmacological agents.

Other neurotransmitters, such as dopamine, have also been implicated as playing a role in OCD. When dopamine antagonists (neuroleptic agents; also called antipsychotics) are added to SRIs, OCD symptoms may improve, especially in patients with comorbid tics or comorbid schizotypal personality disorder (Goodman et al., 1990a; Koran, Ringold, & Elliott, 2000; McDougle, Epperson, Pelton, Wasylink, & Price, 2000; Saxena, Wang, Bystritsky, & Baxter, 1996; Stein, Bouwer, Hawkrigde, & Emsley, 1997). Given the complex interactions and overlap among various receptors in the brain, it is likely that additional neurotransmitters are involved in OCD’s pathophysiology and etiology. Drawing from conflicting results, Baumgarten and Grozdanovic (1998) propose that the orbitofrontal/cingulo-striatal projections are involved in adapting behavior to changing external demands and internal emotional status, a core problem in OCD. The effect of long-term treatment with SRIs may not only be to change the ratio of dopamine to serotonin turnover, but to decrease the sensitivity of various serotonin receptors. Ongoing research will be needed to further elucidate these mechanisms.

**Somatic Treatments**

**General Considerations**

Many forms of somatic therapy—e.g., pharmacological, neurosurgical—have been shown to
be effective for OCD. Behavior therapy is discussed elsewhere in this issue; thus, the focus here will be on pharmacotherapy and other biological treatments.

The general goals of treatment are to reduce the frequency and intensity of symptoms, such as obsessions and compulsions, and to minimize interference in functioning caused by the symptoms. Although a majority of patients experience improvement in symptoms with pharmacotherapy, relatively few patients experience complete remission. Thus, even with treatment, OCD tends to be a chronic illness with a waxing and waning course. Symptoms often worsen during times of psychosocial stress, even when patients are on medication. Thus, anticipating with the patient what stressors may make the symptoms worse can be helpful in long-term treatment.

Compliance, both short- and long-term, can be greatly facilitated by considering how the nature of the illness affects the use of various treatment modalities. For instance, at the core of OCD are the concepts of obsessional doubt, risk aversion, and a need to feel in control of one’s environment. These three features affect both pharmacological and behavioral treatment. In the initial phases of treatment, to address patients’ tendency to doubt and be risk averse, extra time often must be spent conveying the potential efficacy of treatment and lack of serious side effects. Cognitive distortions about both behavior therapy and pharmacological treatment need to be addressed as well. Patients with contamination obsessions and somatic obsessions often have numerous questions about drug safety and may be hesitant to take medication. The clinician must consider this obsessional worry when describing side effects and take special care with the detail with which certain side effects are described, being thorough but not obsessional. It is important when discussing side effects to present an objective assessment of the relative frequency and severity of various side effects.

When prescribing medication, the initial phase of treatment is often most difficult because an adequate therapeutic alliance may not have yet developed. Both risk aversion and a need to be in control may make it difficult for a patient to take medication. Preparing the patient, in advance, about side effects and delayed onset of therapeutic action often helps the patient feel more in control and able to continue treatment. The gradual onset of improvement, although in some cases frustrating, may actually be reassuring to patients who might feel out of control if improvement occurred too rapidly.

**Pharmacological Treatments**

The principal pharmacological agents used to treat OCD prominently affect the serotonin system and include clomipramine, fluoxetine, fluvoxamine, sertraline, paroxetine, and citalopram. Clomipramine is unique among these medications because it has major direct effects on noradrenergic neurotransmitters, which some argue may make it more effective (see below). Because of its direct effects on neurotransmitters other than serotonin, it is often referred to as an SRI; the other agents, which work more selectively on the serotonin system, are called selective serotonin reuptake inhibitors (SSRIs) (although the term SRI applies to the SSRIs as well). The SSRIs are antidepressants that are effective for OCD in addition to depression and many other psychiatric disorders. It appears that non-SRI antidepressants, which also are effective for depression and other disorders, are generally not effective for OCD.

It is critically important to measure symptom severity before and after treatment to judge whether the treatment intervention has worked. The standard measure for OCD treatment is the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989a), a reliable and valid 10-item, 40-point semistructured instrument that assesses the severity of obsessions and rituals during the preceding week. Most studies that have been conducted since
1989 have used the Y-BOCS as one of the major outcome measures. Typically a Y-BOCS score of 16 to 20 is used as a study entry criterion, indicating the presence of clinically significant OCD, although it has been argued that higher scores (e.g., 20 to 21) might reduce the increasing placebo response rates in OCD studies (Greist et al., 1995b). A 25–35% or greater reduction in OCD symptoms on the Y-BOCS is generally considered to represent response to treatment (Goodman et al., 1993). The National Institute of Mental Health Global Obsessive-Compulsive Scale is another frequently used outcome measure. This scale provides a global measure of symptom severity on a 1–15 scale (from minimal to very severe) (Pato & Pato, 1991).

**Clomipramine (Anafranil)** The tricyclic antidepressant clomipramine is perhaps the most extensively studied medication in the treatment of OCD. The 1991 report of the Clomipramine Collaborative Study Group, which contained an extensive review of earlier studies and also reported the findings of the largest double-blind, placebo-controlled trial of clomipramine in OCD (N = 520 patients at 21 sites), found that clomipramine led to significantly greater improvement in OCD symptoms than did placebo. Duration of treatment was 10 weeks, and the mean dosage was approximately 200 mg/day, with the majority of patients (69%) taking 150 to 250 mg/day. More than half (51–60%) of patients receiving clomipramine experienced a 35% or greater reduction in symptoms as measured by the Y-BOCS, compared with only 7–7.5% of the placebo group. The most common side effects were those typical of most tricyclic antidepressants: dry mouth, dizziness, tremor, fatigue, somnolence, constipation, nausea, increased sweating, headache, mental cloudiness, and sexual dysfunction. It should be noted that elderly patients may be more prone to tricyclic side effects, such as orthostatic hypotension, constipation (which may lead to fecal impaction), forgetfulness, and mental cloudiness, which might be confused with dementia. Thus, lower doses may be recommended. The cardiac conduction effects of tricyclic antidepressants may preclude use of clomipramine completely in patients with preexisting cardiac conduction problems, especially atrioventricular block.

Some recent studies of intravenous (IV) clomipramine and citalopram (Pallanti, Quercioli, & Koran, 2002) have been particularly promising. IV administration can produce quicker onset of action and fewer side effects than the oral form and may be effective even in patients who do not respond to oral clomipramine. Like the other SRIs, oral clomipramine usually takes a minimum of 4–6 weeks to produce a clinically significant response. In contrast, in at least one study by Koran, which used IV pulse dosing, patients showed a response within 4.5 days (Fallon et al., 1998; Koran, Sallee, & Pallanti, 1997). The reasons for this rapid response are not fully understood, but it is postulated that the IV preparations avoid first-pass liver and gastrointestinal metabolism, thus leading to increased bioavailability of the parent compound (i.e., clomipramine). This may in turn play a role in rapidly desensitizing serotonergic receptors or initiating changes in postsynaptic serotonergic neurons, which brings about a more rapid clinical response. These preparations are still not approved by the U.S. Food and Drug Administration for clinical use in the United States.

**Fluoxetine (Prozac)** Fluoxetine was the first SSRI available in the United States. While researchers were hopeful that fluoxetine would be more efficacious than clomipramine, controlled double-blind trials have shown it to be equally, but not more, effective than clomipramine (Greist et al., 1995a; Pigott et al., 1990; Wood, Tollefson, & Birkett, 1993).

The fixed-dose trials of fluoxetine are partic-
ularly noteworthy (Tollefson, Birkett, Koran, & Genduso, 1994; Tollefson, Rampey, et al., 1994). These studies indicated that dosages of 20, 40, and 60 mg/day were all effective for OCD when compared with placebo, but there was a trend for 60 mg/day to be more effective. Some patients who did not respond to lower doses responded to higher doses, and others who responded to a lower dose showed further improvement on a higher dose (Tollefson, Rampey, et al., 1994; Wood et al., 1993). Furthermore, patients maintained their improvement or experienced increased improvement during the 5- to 6-month follow-up period (Levine, Hoffman, Knepple, & Kenin, 1989; Tollefson, Rampey, et al., 1994). These were some of the first studies to support long-term treatment of OCD (see Table 1).

Fluoxetine has fewer side effects than clomipramine, perhaps reflecting its more selective mechanism of action. The most common side effects are headache, nausea, insomnia, decreased appetite, anorexia, dry mouth, somnolence, nervousness, tremor, and diarrhea; these side effects tend to be dose related (Tollefson, Rampey, et al., 1994).

**Fluvoxamine (Luvox)** Fluvoxamine became available in the United States in 1995. A number of systematic trials have demonstrated fluvoxamine’s effectiveness in treating OCD (Goodman et al., 1989b; Goodman et al., 1990b; Jenike, Hyman, et al., 1990; Mallya, White, Waternaux, & Quay, 1992). As has been demonstrated with most oral forms of SRIs, a relatively long treatment trial (at least 8–10 weeks) is indicated before concluding that an SSRI is ineffective for OCD (Goodman et al., 1989b). In studies of fluvoxamine, failure to respond at 4 or 6 weeks did not predict response at 10 weeks. In the largest study of fluvoxamine (Goodman, Ward, Kablinger, & Murphy, 1997), even though failure to respond to a previous SSRI was associated with a lower likelihood of responding to fluvoxamine, 6 of 31 patients who had failed a previous trial of clomipramine or fluoxetine did respond to fluvoxamine.

All of the fluvoxamine studies showed a similar side effect profile. Interestingly, insomnia and nervousness tended to occur early in treatment, whereas fatigue and somnolence occurred with ongoing treatment. Other side effects included nausea, headache, and sexual dysfunction (Goodman et al., 1989b, 1990b, 1997; Jenike, Hyman, et al., 1990; Mallya et al., 1992). Overall, however, a small number of patients, only 10–15%, experienced side effects that required medication discontinuation.

**Sertraline (Zoloft)** Similar to other SRIs, sertraline, in a multicenter, fixed-dose, placebo-controlled study of 324 patients, was significantly more effective than placebo, with efficacy similar to that demonstrated for fluoxetine and fluvoxamine in other studies (Greist et al., 1995a, 1995b). As in the fluoxetine studies, there was a trend toward higher doses of sertraline (200 mg/day being more effective than 50 mg/day or 100 mg/day). There was a low dropout rate from side effects (10%); typical side effects included nausea, headache, diarrhea, insomnia, and dry mouth.

A recent study compared the efficacy of sertraline to the non-SRI antidepressant desipramine for patients with OCD and comorbid depression. Although these medications were similarly effective for depression, sertraline was more effective for OCD symptoms. Furthermore, even though desipramine improved depressive symptoms, a significantly greater number of patients treated with sertraline achieved remission from their depression as well as from OCD (Hoehn-Saric et al., 2000).

**Paroxetine (Paxil)** Paroxetine is yet another SSRI with proven efficacy in OCD. Results of a fixed-dose, multicenter trial of 348 patients demonstrated paroxetine’s effectiveness. As was suggested in the sertraline and fluoxetine studies
(Greist et al., 1995b; Tollefson, Rampey, et al., 1994), higher doses (40 or 60 mg/day) may be needed because 20 mg/day was no more effective than placebo (Wheadon, Bushnell, & Steiner, 1993). Paroxetine’s efficacy has been noted to be comparable to that of other SRIs with similar side effects, including lethargy, dry mouth, nausea, insomnia, somnolence, tremor, sexual dysfunction, and decreased appetite (Zohar & Judge, 1996). However, there are also reports of an acute discontinuation syndrome with paroxetine, which can include general malaise, asthenia, dizziness, vertigo, headache, myalgia, loss of appetite, nausea, diarrhea, and abdominal cramps. Occasional patients may experience some of these symptoms when their dose is delayed by only a few hours. Thus, if the medication is discontinued, a more gradual reduction in dose than is typically used with other SRIs is recommended (Barr et al., 1994; Bryois, Rubin, Zbinden, & Baumann, 1998; Dominguez & Goodnick, 1995; Keuthen et al., 1994).

Citalopram (Celexa)

Citalopram has also been shown to be effective for OCD. The chemical structure of citalopram consists of two mirror images, an S (active) form and an R (inactive) form (these forms are known as enantiomers). The S form of citalopram, escitalopram, has recently become available (Lexapro). This S form is purported to have fewer side effects and may have a quicker onset of action in the treatment of depression (Burke, Gergel, & Bose, 2002), although research is needed to determine whether these potential advantages apply to OCD.

Citalopram is unique in its selectivity for serotonin reuptake compared with the other SRIs. Its minimal effect on liver metabolism probably makes it safer than other SRIs when combined with other medications, and it therefore might be an ideal choice for the elderly, who often take medications for other ailments as well. A multicenter, fixed-dose, placebo-controlled trial with 401 patients with OCD showed the typical percentage of patients responding (52% to 65%) in the three dosage groups compared with placebo. The placebo response rate, however, was rather high (37%), as has been seen in more recent OCD medication trials. Similar to other SRIs, there was a trend for a higher dose to have a higher response rate, although there was no statistical difference between the three dosages used (20, 40, and 60 mg/day). Initial side effects included fatigue, sweating, dry mouth, ejaculation failure, nausea, and insomnia, although many patients habituated to these side effects in 4 to 6 weeks. Thus, citalopram may be an excellent choice for OCD treatment because of its side effect profile and low probability of causing drug-drug interactions (Montgomery, Kasper, Stein, Bang Hedegaard, & Lemming, 2001; Richter, 2001).

**Choosing an SRI?**

An important question is whether one SRI is more effective for OCD than the others. To investigate this question, a number of studies have directly compared the efficacy of different SRIs; meta-analyses have also been done. Head-to-head SRI comparison studies have involved clomipramine, fluoxetine (Lopez-Ibor et al., 1996; Pigott et al., 1990), fluvoxamine (Freeman,
Trimble, Deakin, Stokes, & Ashford, 1994; Koran et al., 1996; paroxetine (Zohar & Judge, 1996), sertraline (Bisserbe, Lane, & Flament, 1997), and citalopram (Mundo, Bianchi, & Bellodi, 1997). All found that the SRIs studied were equally efficacious, although all but one (Bisserbe et al., 1997) may have been underpowered, due to small sample size, to detect differences among medications.

However, meta-analyses of OCD trials (Greist et al., 1995a; Greist & Jefferson, 1998; Jenike, Baer, & Greist, 1990), which compare SRIs across large placebo-controlled multicenter trials, lend some support to the notion that clomipramine might be more effective than the more selective agents. In one such study, a four-way (clomipramine, fluoxetine, fluvoxamine, and sertraline) meta-analysis computed effect sizes by comparing the average change in Y-BOCS scores pooled over various studies (Griest et al., 1995a). Clomipramine had the largest effect size. However, like most meta-analyses, these studies are flawed by various factors, including variations in the study protocol, sample size, and the number of treatment-resistant and treatment-naive subjects. Nonetheless, before considering a patient to be treatment resistant, these meta-analyses support use of clomipramine in all patients who do not respond to the more selective SSRIs.

Researchers have hoped that certain OCD symptom profiles might help to predict response to a particular SRI. However, to date, little relevant data are available. Nonetheless, existing data suggest that certain clinical characteristics, such as early age of OCD onset, presence of schizotypal personality disorder, and presence of hoarding, predict poor response to medication (Ackerman, Greenland, Bystritsky, Morgenstern, & Katz, 1994; Alonso et al., 2001; Baer et al., 1992; Eisen et al., 2001; Erzegovesi et al., 2001; Goodman et al., 1997; Mataix-Cols, Rauch, Manzo, Jenike, & Baer, 1999; Ravizza et al., 1995; Stein, Seedat, Shapiro, & Goodman, 2001).

In general, SRIs are well tolerated, although differences in side effect profiles can be considered when choosing one drug over another in particular patients. For instance, potential cardiac arrhythmias can make clomipramine dangerous in overdose or in those with preexisting cardiac arrhythmias. Of all the SRIs, clomipramine is most likely to cause constipation, which can be a particular problem in the elderly. All these agents have the potential to cause sexual side effects, ranging from anorgasmia to difficulty with ejaculatory function. Such side effects may cause noncompliance and yet may not be readily volunteered by patients. It is therefore important for clinicians to ask about sexual side effects. There are a number of treatment strategies for sexual side effects, including dosage reduction, transient drug holidays, and switching to another SRI. Adding certain medications to the SRI (e.g., stimulants, buspirone, sildenafil [Viagra]) may be helpful for some patients. Perhaps most reassuring to patients is that these sexual side effects are not permanent; once the medication is stopped, baseline sexual function returns. In addition, clinical experience suggests that SRIs may lead to improved sexual functioning in some patients, as a result of improvement in OCD symptoms that may have been interfering with sexual functioning.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Usual Dosage</th>
</tr>
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<tbody>
<tr>
<td>Clomipramine</td>
<td>Anafranil</td>
<td>150–250 mg/day</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac</td>
<td>20–80 mg/day</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Luvox</td>
<td>150–300 mg/day</td>
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<tr>
<td>Sertraline</td>
<td>Zoloft</td>
<td>50–200 mg/day</td>
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<tr>
<td>Paroxetine</td>
<td>Paxil</td>
<td>20–60 mg/day</td>
</tr>
<tr>
<td>Citalopram†</td>
<td>Celexa</td>
<td>20–60 mg/day</td>
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*A new form of citalopram made up of the S-enantiomer (eslicitalopram) has recently been marketed as Lexapro, but has not yet been tested in OCD.
† Not presently FDA approved for OCD treatment.
Most of the controlled treatment trials reviewed above have been performed in adults aged 18 to 65. While there are few controlled studies in older and younger populations, extensive clinical experience indicates that these treatments are effective for patients of all ages. In general, children and the elderly tolerate these medications well, although dosage changes and side effects should be carefully attended to. It is generally recommended that, in children, doses be considered based on body weight and thus lower. For instance, a recommended dosage of clomipramine for children is up to 150 mg/day (3 mg/kg/day) versus the 250 mg/day often recommended for adults. Similarly, lower doses should be considered for the elderly, because their decreased ability to metabolize medications can increase the risk of side effects, especially when dose is combined with other medicines they may be taking (Pato & Steketee, 1997; Pato & Zohar, 2001) (see Table 2).

**Treatment for Refractory OCD**

The definition of treatment resistance, or treatment refractoriness, has been discussed at some length in the literature (Goodman et al., 1993; Jenike, 1993; March, Frances, Carpenter, & Kahn, 1997; Stein, 2001). For treatment planning, it is critically important to determine whether a particular patient is truly treatment resistant or has simply received inadequate treatment. A reasonable definition of treatment resistance is failure to respond to several (e.g., 3–4) adequate (in terms of dose and duration) SRI trials without at least 25–35% improvement in Y-BOCS scores, even when augmenting medication or CBT has been added. In such cases, nonpharmacological somatic approaches, such as certain neurosurgical approaches, might be considered (see below, “Neurosurgery and Other Somatic Interventions”), although it is also reasonable to first try additional SRIs. However, a careful treatment history, which includes the patient’s report as well as review of old records, often reveals that the patient has not been adequately treated. An adequate trial of any single pharmacological agent should be a minimum of 10 to 12 weeks and should reach the maximum dose recommended by the manufacturer, if this dose is tolerated by the patient. It should also be determined whether poor compliance may have compromised past pharmacotherapy trials, making them less than adequate. It is also important to determine that past therapy consisted of adequately performed exposure and response prevention for a minimum of sessions with good compliance (e.g., completion of homework) by the patient.

When assessing treatment resistance, it is also important to assess the patient’s diagnosis. Schizotypal personality disorder, borderline personality disorder, avoidant personality disorder, and obsessive-compulsive personality disorder seem to be associated with poorer response to pharmacotherapy, particularly if the personality disorder is the primary diagnosis (Goodman et al., 1993; Jenike, Baer, Minichiello, Schwartz, & Carey, 1986; Stein et al., 2001). Comorbid depression may inhibit the ability to learn and to habituate to anxiety (Jenike, 1993), and thus may make a patient with comorbid depression less likely to respond to behavior therapy until the depression is treated.

**Augmentation Strategies**

When patients partially respond to an SRI, it may be reasonable to augment this response with another agent or CBT, rather than switching to a different SRI (March et al., 1997). However, it is generally thought that if no response occurs with a particular SRI, there is no effect to augment, and therefore switching to another agent should be attempted. No augmentation agent has been firmly established as efficacious. Many appeared promising in open trials, only to
fail in more methodically rigorous trials (Goodman et al., 1993). Many questions about augmentation remain unanswered, including the optimal duration of augmentation, comparative efficacy of different agents, predictors of response, and mechanism of action (Jenike, 1992, 1993). However, since these agents do help some patients significantly, their use should be considered.

One potentially effective strategy in augmentation is to choose agents that are effective for an existing comorbid condition. For instance, a patient with comorbid psychosis or tic disorder may be helped by pimozide (Orap) 1–3 mg/day, haloperidol (Haldol) 2–10 mg/day, and other neuroleptic agents (risperidone [Risperdal] 2–8 mg/day, olanzapine [Zyprexa] 2.5–10 mg/day) (Goodman et al., 1993; Koran et al., 2000; McDougle et al., 1990, 2000; Saxena et al., 1996; Stein et al., 1997) (see Table 1).

**Behavioral Therapy** This issue contains an extensive review of the use of cognitive and behavioral therapy in the treatment of OCD, done in individual, group, and family settings. Yet it would be an oversight to not mention the efficacy of CBT as a pharmacotherapy augmenting agent. Adding CBT to an SRI can improve response to the SRI (Direnfeld, Pato, & Gunn, 2000). Research is beginning to show that combined treatment may be even more effective than either pharmacotherapy or behavioral therapy alone, although these findings are still preliminary (Cottraux et al., 1990; Foa, 1994; Marks, Stern, Mawson, Cobb, & McDonald, 1980; Simpson, Gorfinkle, & Liebowitz, 1999). Some studies have begun to indicate that pharmacotherapy may be particularly helpful in reducing obsessions, whereas compulsions may respond better to behavior therapy (Direnfeld et al., 2000; Hohagen et al., 1998). Clinically, it may be advisable to have patients begin treatment with medication to reduce the intensity of their OCD symptoms (especially if symptoms are severe) and co-morbid depressive symptoms if present, because patients may then be more amenable to experiencing the anxiety that will be evoked by the behavioral challenges they perform. There is no evidence that SRIs interfere with the learning that occurs with behavioral therapy (see Table 1).

**Neurosurgery and Other Somatic Interventions**

Some patients have intractable OCD symptoms even with adequate medication, augmentation, and CBT. In these cases, more aggressive treatment may be warranted. Promising, yet still inadequately tested, experimental treatments include neurosurgery and other procedures, such as deep brain stimulation (DBS) and vagal nerve stimulation (VNS). At present, strict criteria are employed to determine who is eligible for such procedures and to obtain informed consent to perform them (Mindus & Jenike, 1992).

The neurosurgical procedures interrupt brain tracts involved in the serotonin system and implicated in the pathophysiology of OCD. The surgical procedures used include anterior capsulotomy, cingulotomy, and limbic leucotomy, which all aim to interrupt the connection between the cortex and the basal ganglia and related structures (see Neuroanatomical and Neuroimaging Considerations above). These procedures involve making a small lesion of 10–20 mm with either radiofrequency-heated electrodes or, more recently, gamma knife techniques. Gamma knife procedures focus individual gamma rays deep in the brain without causing damage to the skull or surrounding brain tissue through which they pass. DBS and VNS interrupt similar brain tracts; however, these procedures use electrical overstimulation rather than ablation of the nerve cells. Data compiled from a number of small studies have yielded success rates of 25% to 84% with neurosurgical treatments (Mindus & Jenike, 1992; Jenike, 1998), which is promising given the treatment-refractory nature of the...
patients who received these treatments. Results from DBS and VNS are still not available for OCD, since these procedures are new and samples have been small.

Several important findings have come from one of the largest prospective neurosurgical long-term follow-up studies to date, in which all 44 patients received the same neurosurgical procedure (cingulotomy) (Dougherty et al., 2002). Clinical improvement occurred in 32% to 45% of patients, and the average effect size was 1.27 (Cohen's $d$), comparable to that seen in pharmacotherapy trials ($d = 1.09–1.53$). However, these changes were not immediately apparent postoperatively, when most patients were encouraged to receive pharmacotherapy and/or behavioral therapy. Thus, it is unlikely that this response was due to the surgical procedure alone. Because of the longitudinal follow-up, which had a mean duration of 32 months, researchers were able to assess the longer-term impact of the procedure. Particularly noteworthy is that patients continued to show improvement for up to 29 months after surgery without receiving further neurosurgery.

Duration and Discontinuation of Treatment

The question of how long to continue effective medication requires consideration of data from studies of long-term efficacy, maintenance dosing, and treatment discontinuation. This area has received less research attention than has treatment efficacy. One of the largest studies of extended pharmacological treatment used fluoxetine (Tollefson, Rampey, et al., 1994). In this study, two groups comprising 268 patients (70 who had responded to fluoxetine, and 198 who had not responded during an acute 13-week trial) were given the opportunity to continue medication for another 6 months. At the end of the 6 months, most of the 70 patients who had responded initially continued to do well, and over half of the 198 in the nonresponder group experienced a decrease in symptoms when the medication dose was increased from the previous, unsuccessful dose. Similar to previous reports in smaller samples of patients taking fluoxetine (Fontaine & Chouinard, 1989; Frenkel, Rosenthal, Nezu, & Winston, 1990; Levine et al., 1989), this study suggested that symptom improvement was maintained over time and, even more importantly, that further improvement occurred with longer treatment duration and/or higher doses.

In another study, of 85 patients who had been treated with a variety of SRIs, follow-up was done between one year and 3.5 years after initial treatment (Orloff et al., 1994). Not only were 94% of the patients still taking medication, but 87% had maintained previous gains or achieved further improvement. Thus, from a clinical point of view, it seems wise to continue medication for an extended period, perhaps for 6 months to a year or longer after initiating treatment, because not only is improvement maintained during this period, but some patients may experience further improvement. Furthermore, the Orloff study noted that this extended duration of treatment did not result in worsening side effects; in fact, in most cases patients habituated to side effects. The side effects that tend to persist with SRI treatment appear to be fatigue, weight gain, and sexual dysfunction (Rasmussen, Eisen, & Pato, 1993). Similar results have been found with sertraline. In a study of 38 patients on sertraline that included a follow-up period of 2 years, the medication showed continued efficacy and produced fewer side effects with longer-term treatment (Rasmussen, Hackett, & Duboff, 1995).

While improvement may persist, or even increase, with longer-term treatment, the question remains whether doses lower than that at which response occurred can be used in the long term to minimize cost and side effects. Another important question is whether the medication can be discontinued completely. Only a few studies are available that address these issues. Koran et
al. (2002) assessed a large group of patients (N = 223) who had been successfully treated with single-blind sertraline for 52 weeks and were then randomized in a double-blind manner to continued treatment for another 6 months with sertraline or placebo. One third (35%) of the patients in the placebo group relapsed, whereas only 12% of the sertraline group experienced exacerbation. Although the relapse rate was higher with the switch to placebo than sertraline, the relapse rate in the placebo group was surprisingly lower than in earlier studies. Earlier studies in which clomipramine was abruptly discontinued or replaced had relapse rates that were above 90% (Leonard et al., 1991; Pato, Zohar-Kadouch, Zohar, & Murphy, 1988). The authors offered a number of plausible explanations for the sertraline study results, including the possibility that one year of effective treatment may provide sustained benefit for patients, and that patients may have engaged in self-directed behavior therapy, which was not readily available when the clomipramine discontinuation studies were done. They also noted that while OCD symptom ratings did not worsen in the placebo-treated group as a whole, quality-of-life measures showed significant deterioration. This finding points to the need for more sensitive and comprehensive measures of patient improvement in the further exploration of long-term treatment efficacy.

Of interest, some anecdotal data suggest that it may be possible to decrease the dose of medication over the longer term without subsequent relapse (Pato, Hill, & Murphy, 1990). Two more recent studies have more systematically addressed this issue. In one study by Mundo et al. (1997), patients were treated with one third or two thirds of their effective doses of clomipramine or fluvoxamine and did not experience any worsening of symptoms over 102 days. In another study, by Ravizza, Barzega, Bellino, Botutto, and Maina (1996), doses of clomipramine, fluoxetine, or fluvoxamine were halved, without worsening of symptoms over 3 months.

Thus, for patients unable to tolerate medication discontinuation, it may be possible to decrease the SRI dose in longer-term treatment. However, clinical experience indicates that dose reduction may lead to worsening of symptoms, in which case it may be necessary to raise the dose again.

**Conclusion**

For many patients, OCD is a lifelong illness extending from early childhood into adulthood. However, pharmacotherapy, either alone or in combination with behavioral treatment, at adequate doses and duration, offers the majority of patients notable improvement in symptoms and functioning. Other biological procedures for the truly treatment refractory patient are currently being investigated and remain experimental at this time. More research is needed to identify predictors of treatment response to various medications and to better guide clinicians in choosing a single treatment modality versus a combination of medications and CBT. Further research is also needed on effective SRI augmentation strategies and on optimal doses and treatment duration to prevent relapse and symptom exacerbation.

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**References**


Direnfeld, D., Pato, M. T., & Gunn, S. (2000, May). *Behavior therapy as adjuvant treatment in OCD*. Poster presentation at APA annual meeting, Chicago, IL.


center double-blind comparison of sertraline and desipramine for concurrent obsessive-compulsive and major depressive disorders. *Archives of General Psychiatry*, 57, 76–82.


Montgomery, S. A., Kasper, S., Stein, D. J., Bang Hedegaard, K., & Lemming, O. M. (2001). Citalopram 20 mg, 40 mg, and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. *International Clinical Psychopharmacology*, 16, 75–86.


Wheadon, D., Bushnell, W., & Steiner, M. (1993, December). A fixed dose comparison of 20, 40, or 60 mg paroxetine to placebo in the treatment of obsessive-compulsive disorder. Paper presented at the annual meeting of the American College of Neuropsychopharmacology, Honolulu, HI.
