

# Obsessive-Compulsive Disorder: Strategies for Optimal Treatment

**T**his ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry presents the highlights of the planning teleconference series “Obsessive-Compulsive Disorder: Strategies for Optimal Treatment,” which was held in May and June 2008. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Jazz Pharmaceuticals.

The planning teleconference series was chaired by **Eric Hollander, M.D.**, from the Department of Psychiatry, Mount Sinai School of Medicine, and the Seaver and New York Autism Center of Excellence, New York. The faculty were **Jonathan S. Abramowitz, Ph.D., ABPP**, from the Departments of Psychology and Psychiatry, and the Anxiety and Stress Disorders Clinic, University of North Carolina, Chapel Hill; **Lorrin M. Koran, M.D.**, from the Department of Psychiatry and Behavior Sciences, Stanford University School of Medicine, Stanford, Calif.; and **Stefano Pallanti, M.D., Ph.D.**, from the Department of Psychiatry, Mount Sinai School of Medicine, New York, N.Y.

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## Psychological Approaches to Understanding the Nature, Etiology, and Treatment of Obsessive-Compulsive Disorder

Although the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision, (DSM-IV-TR),<sup>1</sup> states that a diagnosis of obsessive-compulsive disorder (OCD) requires that patients have obsessions or compulsions, patients usually experience both obsessions and compulsions, explained Jonathan S. Abramowitz, Ph.D., ABPP. In his presentation, Dr. Abramowitz described the symptoms, dimensions, etiology, psychological theories, and psychosocial treatment of OCD.

### Understanding Obsessions

*Obsessions* are unwanted persistent thoughts, impulses, or images that are experienced as intrusive, inappropriate, and distressing; they are anxiety-provoking, but not simply excessive worries about real-life problems. The patient usually recognizes that obsessions are a product of his or her own mind and tries to ignore, suppress, or neutralize obsessions by replacing them with another thought or action (compulsions).

**Common obsessions.** Among the examples of common obsessions, contamination is likely the most prevalent obsession, said Dr. Abramowitz. Contamination obsessions may involve a fear of dirt, germs, bodily waste, or chemicals. Patients may be afraid that they will become ill due to contamination or that they will infect others; and some just fear the idea of germs being present rather than causing illness. Another common obsession involves a fear of making mistakes that will have serious consequences, such as harm to others or themselves; patients may

worry about locks, appliances, paperwork, or decisions. Obsessions about having or acting on unwanted impulses, which may be violent, sexual, religious, or embarrassing, are also common. In addition, patients often have obsessions involving order, e.g., neatness, symmetry, or numbers; they may worry that if everything is not in a certain order, a catastrophe will occur.

**Obsessions versus worries and ruminations.** Obsessions are not the same as worries, emphasized Dr. Abramowitz. While worries involve real-life problems, obsessions typically do not. Worries tend to involve verbal content, whereas obsessions tend to also involve images or impulses. In addition, psychophysiologic reactivity, such as increased heart rate and skin conductance, often occurs with obsessions but not with worries.

Dr. Abramowitz stated that obsessions should also be differentiated from depressive ruminations, which are general, pessimistic ideas regarding one's self and the world. Obsessions are usually fears about specific disastrous consequences, with infrequent content shifts, while the content of ruminations shifts frequently and is nonspecific. Also, obsessions elicit neutralizing responses, while ruminations do not.

### Understanding Compulsions

Dr. Abramowitz described *compulsions* as repetitive behaviors or mental acts that a person feels driven to perform as a neutralizing response to an obsession or according to rigid rules; they are intended to reduce anxiety or prevent some kind of feared

consequence and are not randomly performed. Compulsions are either unrealistic or clearly excessive thoughts or acts.

**Common compulsions.** Compulsive behaviors include repetitive hand-washing, cleaning, arranging, and checking. For example, a patient may frequently check locks to neutralize the fear of making a mistake by leaving the door open. Compulsive thoughts include creating mental images of “safe” words or numbers in response to seeing “bad” words or numbers, silently repeating special prayers in a set manner, and mentally counting, making lists, or reviewing one’s actions. Often, mental rituals are confused with obsessions because both present as thoughts.

### Dimensions of OCD

Research<sup>2</sup> supports the classification of OCD symptoms into different dimensions based on the prevailing theme. Dr. Abramowitz stated that the dimensions of OCD include the previously discussed themes of contamination, harm and mistakes, symmetry and order, and unacceptable thoughts, as well as hoarding. Most patients cannot be precisely classified into one category, as they may have symptoms of multiple dimensions, added Dr. Abramowitz. Until recently, hoarding, which involves excess saving or collecting of items and a fear of discarding these items, has been considered a dimension of OCD, but recent research<sup>3</sup> casts doubts on the idea that hoarding is related to OCD.

### Etiology of OCD

The exact cause of OCD is unknown but, most likely, is a combination of biological/genetic factors and learning/environmental factors; the cause may vary between individuals, explained Dr. Abramowitz. Although there is little evidence that an “OCD gene” exists, certain people may have a genetic predisposition to anxiety or what has been referred to as *neuroticism*. Individuals may possess this vulnerability to anxiety, and then learning

or environment influences the expression of OCD symptoms.

Dr. Abramowitz asserted that from a psychological perspective, patients with OCD are thought to learn a certain way of thinking, called a *cognitive style* or a *core belief*, concerning interpretations of thoughts and situations (e.g., overestimates of danger, over-importance of intrusive thoughts, exaggerated sense of responsibility). This cognitive style is thought to be learned in various ways, including direct observation, personal experiences, and informational transmission (such as through the media). For example, a person may hear about how dangerous germs are and begin to obsess about germs.

### Theories of OCD and Psychological Treatment

Until the 1960s, OCD was considered to be treatment-resistant, so those who had the disorder would likely suffer for their entire lives, stated Dr. Abramowitz. Psychodynamic therapy, which aims to help patients better understand unconscious conflicts, was not an effective long-term treatment as it rarely lessened symptoms. Then, through the 1960s, 1970s, and 1980s, cognitive and behavioral models of OCD were developed, and cognitive-behavioral therapy (CBT), which was derived from cognitive and behavioral models of the disorder, became available for the treatment of OCD.

**Theories of OCD.** Dr. Abramowitz discussed 2 theories of OCD—the learning theory model and the cognitive model. These theories are the basis for CBT.

The learning theory model of OCD states that obsessions cause anxiety or distress, and compulsions reduce this anxiety. However, the performance of the compulsive rituals to relieve the obsessive anxiety prevents the natural extinction of the anxiety. When the anxiety returns, the compulsions are negatively reinforced by the immediate, although brief, reduction of anxiety they engender.<sup>4,5</sup> Behavioral therapy for OCD is based on the learn-

ing theory model and incorporates exposure and response prevention.

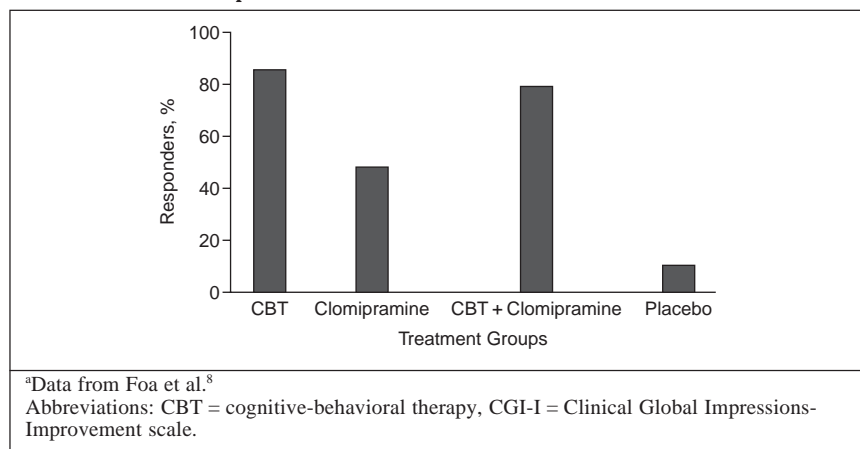
The cognitive model of OCD states that intrusive, unpleasant thoughts are normal; however, obsessions develop if these unwanted thoughts are interpreted as being highly significant (e.g., thoughts are equivalent to actions). Misappraisal of these thoughts as important increases anxiety and leads to neutralizing behavior (compulsions). Paradoxically, neutralizing increases the frequency of obsessions and prevents disconfirmation of the mistaken appraisals.<sup>6</sup> Cognitive therapy involves altering the patient’s beliefs and interpretations of the importance of the unwanted intrusive thoughts.

**Components of CBT.** The delivery of CBT includes exposure and cognitive therapy, which weaken the anxiety associated with obsessive thoughts, and response prevention, which diminishes the pattern of performing rituals to reduce anxiety. Dr. Abramowitz stated that the current absence of a definitive causal model for OCD does not affect treatment outcomes because CBT is based on understanding the factors that maintain obsessions and compulsive rituals rather than understanding their origins.

Two types of exposure are used during cognitive-behavioral treatment—exposure in vivo and imaginal exposure. During in vivo or situational exposure, patients practice prolonged confrontation with their anxiety-evoking stimuli; this technique requires patients to face their fears. For example, someone with contamination-themed OCD may practice touching money that has fallen on the floor, and even touching the floor itself until the associated anxiety starts to decrease naturally. In imaginal exposure, patients must imagine the anxiety-evoking stimuli and mentally confront feared disasters. An example of imaginal exposure is purposely envisioning illness caused by contamination, explained Dr. Abramowitz.

Other components of CBT are response prevention and cognitive therapy. Response prevention requires

**Figure 1. Completer Response Rates as Determined by CGI-I Scores in a 12-Week Randomized, Placebo-Controlled Trial Comparing CBT, Clomipramine, and CBT Combined With Clomipramine<sup>a</sup>**



the patient to resist performing compulsive rituals. For example, after touching the floor, the patient must resist washing his or her hands. Cognitive therapy involves psychoeducation and discussion of mistaken cognitions. The goal is to help patients understand that they are misinterpreting normal, intrusive thoughts, said Dr. Abramowitz.

### Efficacy of CBT

Research has indicated that CBT is more effective than waiting list<sup>7</sup> or pill placebo,<sup>8</sup> progressive muscle relaxation,<sup>9</sup> anxiety management training,<sup>10</sup> and serotonergic medications.<sup>8</sup> Four

randomized, controlled studies<sup>7-10</sup> showed substantial improvement in symptoms as measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS) following CBT. In a 12-week trial, Foa et al.<sup>8</sup> compared CBT, clomipramine, their combination, and placebo in patients with OCD. Among patients who completed the trial, the group with the greatest proportion of responders was the CBT group (Figure 1). Dr. Abramowitz added that CBT has been found to be effective outside of the select populations in controlled trials. Franklin et al.<sup>11</sup> observed symptom reduction in a sample of non-randomized, clinical outpatients that

was comparable to that found in 4 randomized controlled trials.

**Predicting outcomes.** Some variables may affect the efficacy of CBT in patients with OCD. Dr. Abramowitz and colleagues<sup>12</sup> assessed the effect of session frequency—daily for 3 weeks versus twice-weekly for 8 weeks—on CBT outcomes and found no significant difference between programs; both were effective. However, a meta-analysis of 38 trials<sup>13</sup> suggested that exposure sessions supervised by a therapist were more effective than exposure sessions conducted by the patients on their own. Dr. Abramowitz also found that patients with hoarding symptoms tend to have poorer outcomes with CBT than patients with any other symptom subtype.<sup>2</sup> As mentioned, hoarding may be outside of the realm of OCD, which would explain lack of response to OCD treatments. Other negative predictors of CBT outcome are severe depression<sup>14</sup> and poor insight.<sup>15</sup>

### Conclusion

Dr. Abramowitz concluded that by understanding the symptoms, dimensions, and theories of OCD, clinicians may achieve better treatment outcomes. Cognitive-behavioral therapy should be considered for both acute and long-term treatment, because studies support its efficacy.

## The Burden and Impact of OCD on Patients, Families, and Society

Social functioning, work functioning, mental health, and family relationships are frequently impaired by OCD, leading to a diminished quality of life for patients and their families. Lorrin M. Koran, M.D., stated that although the term *quality of life* (QoL) has no universal definition in medical research and different instruments are used to measure QoL, health-related QoL is commonly studied in terms of physical functioning, degree of physical pain, interpersonal relationships, social role functioning, mental health, and perceived health. Dr. Koran re-

viewed the impact of OCD on patients' lives and the effects of treatment on QoL.

### Effect of OCD on Social Role Functioning

Social role functioning encompasses a person's performance in social activities as well as in work or school responsibilities. Dr. Koran and colleagues<sup>16</sup> found that 22% of OCD patients enrolled in a medication trial were unemployed (versus 6% for the general U.S. population). Leon et al.<sup>17</sup> found that men with OCD were more

likely to be chronically unemployed and receiving disability or welfare aid at rates higher than the general population. In addition, a recent study<sup>18</sup> found that 38% of patients with OCD reported that their psychiatric symptoms rendered them unable to work. Symptom severity was found to be the most powerful predictor of occupational disability. Another aspect of social functioning is living with a spouse. One study<sup>19</sup> found that nearly 40% of adult patients with OCD had never been married, and 25% of the patients were living with their parents; both

figures significantly higher than in the general population.

### Effect of OCD on Mental Health

In addition to diminished social and work functioning, patients with OCD are at increased risk for developing other psychiatric disorders, which also impair QoL, explained Dr. Koran. Specifically, the current prevalence of major depression in patients with OCD has been reported in clinical studies to be 14% to 40%, and the lifetime prevalence 36% to 55%.<sup>20</sup> Clinical studies have also reported a lifetime prevalence of bipolar disorder ranging from 3% to 18%.<sup>20</sup> The current prevalence of anxiety disorders in patients with OCD has been found to be 15% to 31%; of alcohol dependence, up to 20%; and of drug dependence, as much as 13%.<sup>21</sup>

Another measure of the effect of OCD on patients' mental health is the rate of suicidality, stated Dr. Koran. In a U.S. epidemiologic study,<sup>22</sup> people with OCD had a higher rate of suicide attempts than people with other psychiatric disorders or no disorders. In a British epidemiologic study,<sup>21</sup> one fourth of participants with OCD had attempted suicide. A study of Brazilian clinic patients<sup>23</sup> found that 70% had thought that life was not worth living, 20% had made suicidal plans, and 10% had made a suicide attempt; current suicidal ideation was found in 14% of the patients. Another study,<sup>24</sup> which examined OCD clinic patients in India, reported that 28% were currently experiencing suicidal ideation and 27% of patients had made a suicide attempt; depression and hopelessness correlated with a high risk of suicidal behavior.

### Effect of OCD on Family

Dr. Koran indicated that OCD not only affects the patient in many ways but also affects the QoL of the patient's family. In fact, 60% to 88% of patients may involve family members in performing their rituals.<sup>25,26</sup> Family may be asked to provide repeated reassurance to the patient or to take over some of the patient's family responsibilities.

**Table 1. Accommodations Made During Past Month By Spouses or Parents of Patients With Obsessive-Compulsive Disorder (OCD)<sup>a</sup>**

Modifications Made	Degree of Accommodation, %				
	Not at All	Mild	Moderate	Severe	Extreme
Family routine	64.7	0.0	17.6	2.9	14.7
Work schedule	79.4	8.8	2.9	5.9	2.9
Leisure activities	47.1	11.8	23.5	17.6	0.0
Avoidance of things, places, or people	58.8	17.6	14.7	0.0	8.8

<sup>a</sup>Adapted with permission from Calvocoressi et al.<sup>25</sup>

Failure to comply with these requests may result in angry outbursts from patients or in guilt felt by family members.<sup>25</sup>

A few studies<sup>25,27</sup> have measured the effect of patients' OCD on the QoL of family members. Magliano et al.<sup>27</sup> found that 74% of relatives of patients with OCD had compromised social relationships, and 84% had feelings of depression. Calvocoressi et al.<sup>25</sup> interviewed the spouses or parents of individuals with OCD and reported modified family routines, work schedules, leisure activities, and the avoidance of certain activities or people because of the patient's OCD (Table 1).

Dr. Koran emphasized that the impaired family relationships resulting from the patient's OCD symptoms may adversely affect rates of help-seeking, treatment compliance, and treatment response. In contrast, family education, support, and participation in treatment may promote favorable treatment outcomes and reduced family suffering. Dr. Koran cited [www.OCFoundation.org](http://www.OCFoundation.org) as a good source for additional education and support for family members.

### Effect of OCD Treatment on Health-Related QOL

Dr. Koran reviewed studies that examined the effects of various treatments on the health-related QoL of patients with OCD. In 1980, Marks and colleagues<sup>28</sup> conducted a randomized, controlled study in which patients with OCD received either clomipramine or placebo for 8 months. In the fourth to seventh weeks, the 2 treatment groups were randomly assigned to relaxation treatment or exposure in vivo;

in weeks 7 to 10, both treatment groups received exposure in vivo. After 10 weeks, both treatment groups experienced improved social/family functioning, leisure activities, and sexual life. A follow-up study<sup>29</sup> reported reduced rituals (especially in patients who had more exposure) and improvement on assessor-rated measures of work, family, sex, leisure, and social functioning 1.25 years after completing the 8 months of treatment. Since this report did not document treatment received after the initial 8-month study period, the reasons for the improved health-related QoL ratings cannot be determined.

More recently, Moritz et al.<sup>30</sup> examined QoL in a heterogeneous sample of 79 patients with OCD (outpatients, inpatients, and patients in partial hospitalization programs). Participants received CBT, and 41% of the patients also received a selective serotonin reuptake inhibitor (SSRI) at some point during treatment. After 8 to 10 weeks, QoL was assessed in those who completed treatment (78%). Participants reported improvements in social and physical functioning, general health, vitality, role limitations due to emotional problems, and mental health (anxiety and depression). Responders to treatment had more improvement in QoL than nonresponders. However, for each area of functioning, except for the physical categories, at least 50% of OCD patients had QoL scores that remained below the 25th percentile of a healthy subsample of the German population. So, Dr. Koran explained, although QoL improved for most patients, it was still considerably impaired.

Another short-term study<sup>31</sup> found that QoL improved after pharmacotherapy for OCD but that improvement in symptoms was not associated with improvement in QoL. Thus, the study concluded that improvement was due to participation in the trial, not to the effects of the medication. Longer treatment and longer observation periods may be needed, however, to clarify the effects of OCD treatment on OCD patients' QoL.

### Conclusion

Dr. Koran concluded that OCD not only affects patients but also their families and, as a result, society at large. Fortunately, research suggests that successful treatment not only reduces OCD symptom severity but also leads to improved QoL.

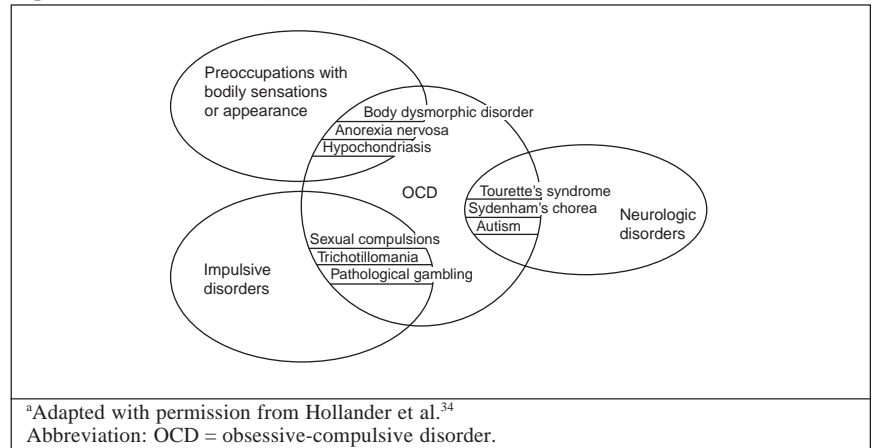
## Neurobiology and Psychopharmacology of Obsessive-Compulsive and Spectrum Disorders

Obsessive-compulsive spectrum disorders (OCSs) are illnesses that have similar symptoms (such as repetitive behaviors), neurobiology, and treatment responses to those of OCD.<sup>32</sup> Eric Hollander, M.D., described the classification, neurocircuitry, and pharmacologic treatment of these disorders.

### Classification of OCSs

While planning for the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, (DSM-V), Dr. Hollander and colleagues established criteria for OCSs. Specifically, to be classified as an OCS, the disorder must share 3 of the following 5 OCD characteristics: (1) course and phenomenology, e.g., obsessions and/or compulsions; (2) comorbidity; (3) family history; (4) brain circuitry; and (5) treatment response. One of the 3 met criteria must reflect underlying etiology or pathophysiology, meaning that either family history or brain circuitry must be shared between OCD and the

**Figure 2. Obsessive-Compulsive Spectrum Disorders<sup>a</sup>**



disorder. Dr. Hollander divided the disorders within the spectrum into 3 groups: disorders that involve preoccupations with bodily sensations or appearance, impulsive disorders or behavioral addictions, and neurologic disorders (Figure 2).

### Neurocircuitry of OCD

Dr. Hollander explained that the basic brain circuitry of OCD involves increased metabolic activity in the orbitofrontal cortex, the basal ganglia or striatum, regions such as the head of the caudate and the globus pallidus, the thalamus, and regions like the anterior cingulate cortex. Thus, Dr. Hollander stated, OCD is essentially hyperactivity involving cortical-striatal-thalamic circuits. Successful treatment of OCD with medication and/or psychotherapy is associated with decreased activity of these circuits. For example, treatment may be associated with decreased activity in the head of the caudate early on, and, over time, decreases might be seen in orbitofrontal activity.

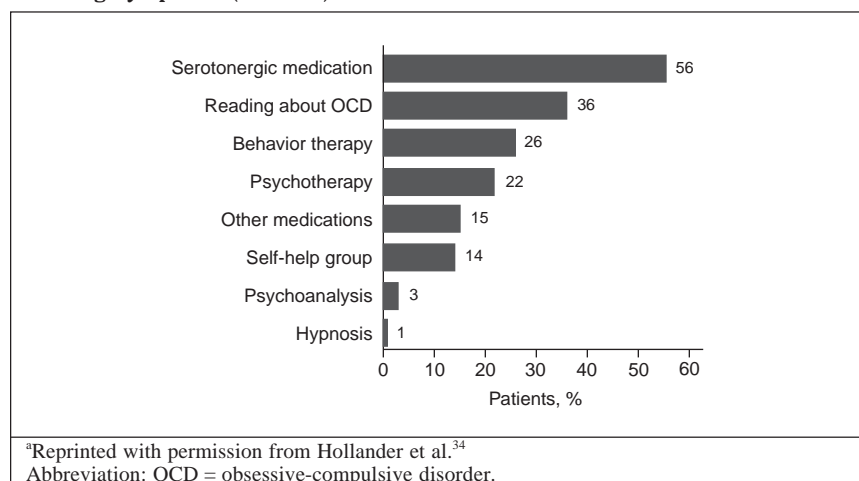
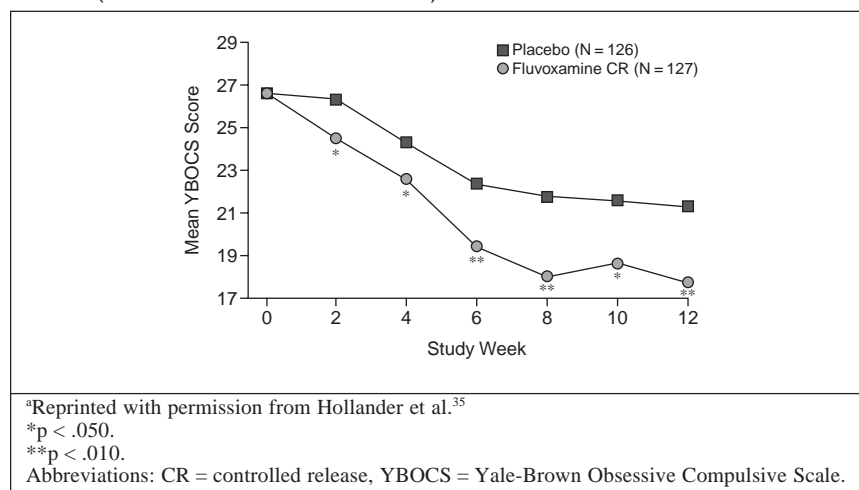
The brain circuitry of OCD, added Dr. Hollander, differentiates it from other anxiety disorders and conditions. In other anxiety disorders, the amygdala plays a central role in fear and anxiety.

Subtle differences in the brain circuitry of patients with OCD account for the differences in the expression of clinical symptoms. For example, stated

Dr. Hollander, motoric behaviors and tic-like dysfunction are associated with a greater involvement of the dorsolateral prefrontal cortex as well as dorsal regions of the caudate, the globus pallidus internus, and the thalamus; whereas, repetitive impulsive behaviors often involve activation of regions like the anterior cingulate, directly leading to the shell of the nucleus accumbens, the globus pallidus internus, and the thalamus. Because the nucleus accumbens shell plays a key role in goal-directed, motivated behavior toward future reward, the impairment of circuits that go through the nucleus accumbens is associated with impulses and addictive, repetitive behaviors.

### Psychopharmacology of OCD

**Mechanisms.** In the past, explained Dr. Hollander, research focused a great deal on serotonergic mechanisms of OCD and related disorders. Serotonin reuptake inhibitors (SRIs) such as clomipramine were effective in reducing the severity of thoughts and behaviors,<sup>33</sup> which was probably the most potent evidence for the involvement of the serotonin system in OCD. Recently, interest has grown regarding the involvement of the dopamine system in OCD; this interest is based on the idea that, in animal models, dopamine neurons in the midbrain appear to fire a great deal in situations of uncertainty. Also, atypical antipsychotics,

**Figure 3. Percentage of OCD Sufferers Who Found Treatments Helpful in Reducing Symptoms (N = 419)<sup>a</sup>****Figure 4. Mean YBOCS Total Scores During Treatment With Fluvoxamine CR or Placebo (last observation carried forward)<sup>a</sup>**

which can be used as augmentation in treatment-resistant OCD, block central dopamine receptors and may be helpful in blocking midbrain dopamine receptors. When combined with SSRIs, atypical antipsychotics may increase dopamine release in prefrontal regions. In addition, over time, the compulsive habits or rituals performed by patients can be associated with reinforcement or reward, which also links OCD with dopamine mechanisms. Dr. Hollander emphasized that in addition to therapy, it is important to encourage patients to engage in meaningful activities, which may involve prefrontal dopamine

mechanisms and help patients to focus their attention on something other than their disorder.

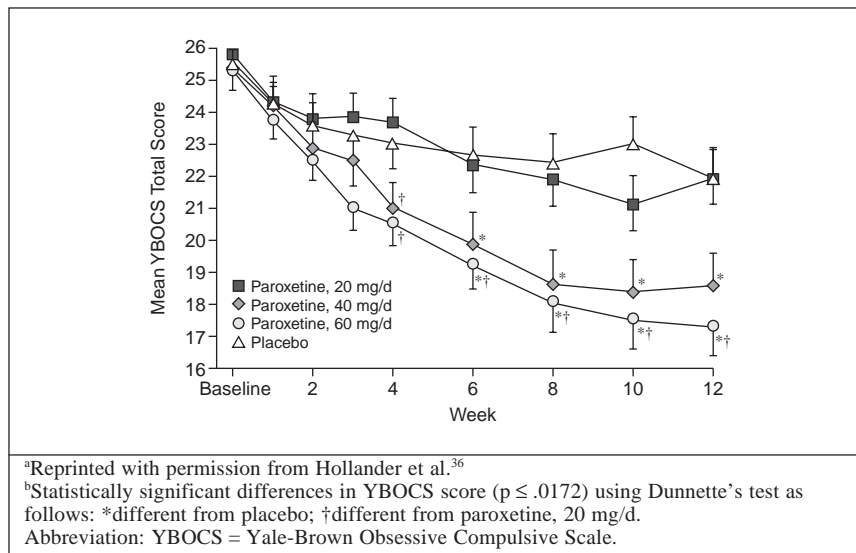
**Treatments.** Although OCD can be successfully treated, patients may wait up to 10 years before seeking help, and several more years may pass before they receive the correct diagnosis.<sup>34</sup> Appropriate recognition and treatment are essential to resolving the patient's impaired functioning and reduced QoL. Dr. Hollander and colleagues<sup>34</sup> surveyed patients with OCD to determine which treatments were helpful in reducing symptoms. The most effective treatments, according to these patients,

were serotonergic medication, reading about OCD, and behavior therapy (Figure 3). Several SSRIs are approved by the U.S. Food and Drug Administration (FDA) for treating OCD, including fluvoxamine, fluoxetine, sertraline, paroxetine, and clomipramine.

Dr. Hollander stated that research supports the selective efficacy of serotonergic agents for treatment of OCD. For example, Goodman et al.<sup>33</sup> compared the efficacy of fluvoxamine, an SSRI, to that of desipramine, a norepinephrine reuptake inhibitor, in patients with OCD. Over an 8-week period, SSRI-treated patients had superior improvement of symptoms according to YBOCS scores. Response was found in 52% of the patients taking fluvoxamine and 11% of patients taking desipramine. So, added Dr. Hollander, although norepinephrine reuptake inhibitors are often effective for the treatment of other anxiety disorders, they are not very effective in OCD.

Another study<sup>35</sup> measured the efficacy and safety of controlled-release (CR) fluvoxamine (100–300 mg/day) in patients with OCD. At week 2 of the 12-week study, fluvoxamine CR was significantly superior to placebo in reducing YBOCS total score; this early response continued throughout the trial (Figure 4). However, statistically significant results regarding compulsions were not achieved until week 6, which suggests that SSRIs have a more rapid onset for obsessions than for compulsions. Dr. Hollander cited a 3-phase study<sup>36</sup> that assessed the acute and long-term efficacy of the SSRI paroxetine (20–60 mg/day) in OCD patients. The acute phase of the study found that patients who were treated with 40 mg/day or 60 mg/day of paroxetine for 12 weeks experienced significant improvement on YBOCS total score compared with placebo (Figure 5), which suggests a dose-response relationship with some SSRIs. In the open-label continuation phase, patients who were classified as early responders in the acute phase continued to respond over 6 months, according to YBOCS total scores. In the 6-month

**Figure 5. Phase 1: Mean YBOCS Total Scores During Treatment With Paroxetine or Placebo (observed cases analysis)<sup>a,b</sup>**



maintenance phase, patients who were switched from paroxetine to placebo were 2.7 times more likely to relapse than those who were continued on the medication ( $p \leq .033$ ). Dr. Hollander suggested that patients who respond to SSRIs in the acute phase will continue to do well if continued on the medication, whereas some patients will relapse if the medication is discontinued. Because OCD is not an episodic disorder

but rather is chronic, patients typically have better results over time when kept on medication.

Although a dose-response relationship may exist with paroxetine, explained Dr. Hollander, this does not appear to be the case with sertraline. Greist et al.<sup>37</sup> assessed the efficacy of sertraline (50–200 mg/day) over 12 weeks in patients with OCD and found no dose-response relationship. Patients

who were given 50 mg/day or 200 mg/day of sertraline improved on all 3 measures of efficacy, while those who were given 100 mg/day improved on 1 scale. However, Rasmussen et al.<sup>38</sup> found that patients who were early responders to acute treatment with sertraline maintained that response over 2 years when kept on the medication.

Montgomery et al.<sup>39</sup> assessed the efficacy of citalopram (20, 40, or 60 mg/day) over 12 weeks in patients with OCD. All of the doses significantly improved YBOCS scores compared with placebo ( $p < .01$ ) and no significant difference was found between doses. The medication was well-tolerated.

## Conclusion

Dr. Hollander concluded that the classification of OCDs should help clinicians screen for all of the disorders as a group. Treatment of these disorders is often challenging, because patients may not respond to the first or even several trials with an SSRI, and other strategies may need to be employed. By accurately identifying these disorders and individualizing treatment, clinicians may be able to lessen the gap that currently exists between symptom development and successful treatment.

## Management of Treatment-Resistant OCD

Because many patients respond to treatment with SRIs, OCD is often deemed a serotonergic dysfunctional disorder. However, despite the selective efficacy of SRIs in OCD,<sup>33,40</sup> Stefano Pallanti, M.D., Ph.D., explained that about half of patients with OCD do not respond to serotonergic medications.<sup>41</sup> Dr. Pallanti discussed diagnostic implications of treatment resistance as well as strategies for identifying and treating nonresponsive patients.

### Implications for the OCD Diagnosis

Dr. Pallanti stated that the concept of nonresponse implies a mismatch between a diagnostic classification and

a treatment. While diagnostic instruments are used to define clinical entities, these classifications are often treatment-oriented, because they correlate with the results of clinical trials. When faced with numerous nonresponsive patients, as in OCD, clinicians and researchers must consider whether the current diagnostic boundaries hold firm or need to be reassessed.

### Identifying Treatment Resistance

**Defining stages of response.** Dr. Pallanti stated that standard definitions of *remission*, *partial response*, and *nonresponse* are needed in the field to better assess the progress of patients and to generalize between studies. Dr.

Pallanti and colleagues proposed specific definitions for stages of response in OCD (Table 2).<sup>41</sup>

#### **Predictors of treatment resistance.**

Dr. Pallanti explained that certain characteristics are predictors of treatment-resistant OCD. In adults, these include a longer duration of illness, comorbidities, comorbid personality dysfunctional traits (obsessive-compulsive trait of personality disorders), comorbid depression, and comorbid social anxiety. In children, these characteristics include comorbid ADHD, comorbid tics and/or Tourette's syndrome, and comorbid oppositional defiant disorder. Family attitudes regarding symptoms may also contribute to the

**Table 2. Proposed Stages of Response in Obsessive-Compulsive Disorder (OCD)<sup>a</sup>**

Stage of Response	Stage	Description
I	Recovery	Not at all ill; < 8 on YBOCS
II	Remission	< 16 on YBOCS
III	Full Response	≥ 35% reduction of YBOCS and CGI 1 or 2
IV	Partial Response	> 25% but < 35% YBOCS reduction
V	Nonresponse	< 25% YBOCS reduction, CGI 4
VI	Relapse	Symptoms return (CGI 6 or 25% increase in YBOCS from remission score) after 3+ months of "adequate" treatment
VII	Refractory	No change or worsening with all available therapies

<sup>a</sup>Reprinted with permission from Pallanti et al.<sup>41</sup>  
Abbreviations: CGI = Clinical Global Impression Scale, YBOCS = Yale-Brown Obsessive Compulsive Scale.

likelihood that children will have treatment-resistant OCD.

### Treatment Strategies

Dr. Pallanti discussed multiple strategies for treatment of resistant OCD. Pharmacologic options included hyperdosing, augmenting, or combining SSRIs; augmenting SRIs with antipsychotics; and potentially using newer treatments, both pharmacologic and neurophysiologic.

**Serotonergic strategies.** In some cases, SSRIs are effective for treatment of OCD, but Dr. Pallanti noted that they are not effective enough because many patients do not achieve remission. In addition, a higher dosage is required for the treatment of OCD than that which is necessary to completely occupy the serotonin transporter in most brain regions. Blier et al.<sup>42</sup> argued that the higher dosages and delay in onset of action can be accounted for by the greater delay in downregulation of the serotonin-1B (5-HT<sub>1B</sub>) receptors in the orbitofrontal cortex and the subsequent stimulation of the 5-HT<sub>2A</sub> receptors. The addition of 5-HT<sub>2A</sub> receptor antagonists (such as atypical antipsychotics) can hasten or augment the effects of SSRIs. However, first-line treatment for resistant OCD still involves serotonergic medication.

The first strategy that Dr. Pallanti suggested for treatment of resistant OCD was a hyperdose of an SSRI. Research<sup>43</sup> has supported the efficacy of high-dose escitalopram for resistant OCD.

Another suggested option was to augment SSRIs with clomipramine. In a 90-day open trial, Pallanti et al.<sup>44</sup> compared the efficacy of citalopram monotherapy with that of the combination of citalopram and clomipramine in patients with treatment-resistant OCD. The study found that patients treated with citalopram and clomipramine showed significantly more improvement in YBOCS scores than patients treated with citalopram monotherapy.

Intravenous serotonergic treatment was a third strategy suggested by Dr. Pallanti. One 3-week open study<sup>45</sup> found that patients who were unresponsive to oral treatment with SRIs experienced rapid relief of OCD symptoms and improved QoL with intravenous citalopram treatment. In addition, Fallon et al.<sup>46</sup> found that intravenous clomipramine treatment was more effective than placebo for patients with OCD who were unresponsive to oral clomipramine. More recently, pulse-loading seemed to induce more rapid and greater improvement than expected in treatment-resistant OCD. Further investigation of oral pulse-loading regimens in treatment-resistant OCD is warranted.<sup>47</sup>

An additional suggested treatment was combining SSRIs, an option that has not been examined in clinical trials but, according to Dr. Pallanti, is common in clinical practice. This suggestion is based on the rationale that, because each SSRI has a unique serotonergic profile, combining agents may produce therapeutic synergy.

Dr. Pallanti noted that a caveat to prescribing high doses of SSRIs or combining serotonergic agents is that clinicians should use caution to avoid serotonin syndrome.

**Dopaminergic agents.** As second-line treatment for resistant OCD, Dr. Pallanti recommended adding an antipsychotic to the current SSRI because of its dopamine-2 (D<sub>2</sub>) receptor affinity. Clomipramine, fluoxetine, and fluvoxamine may be the best SRIs to be considered for use with antipsychotic augmentation,<sup>48</sup> especially in low doses, but more evidence is needed.

A recent meta-analysis<sup>49</sup> of 9 studies involving 278 patients with treatment-resistant OCD found sufficient evidence to support the efficacy of augmentation with haloperidol or risperidone; however, the efficacy of augmentation with olanzapine or quetiapine could not be determined, and more studies are needed. The subgroup of OCD patients with comorbid tics appeared to especially benefit from antipsychotic augmentation. However, only one third of the total sample had a meaningful response to the antipsychotic augmentation.

Studies<sup>50-52</sup> have examined the mechanisms of action of antipsychotic augmentation in OCD. For example, Keuneman et al.<sup>50</sup> concluded that the efficacy of adjunctive antipsychotics with SRIs in refractory OCD may be due to direct D<sub>2</sub> blockade separate from or together with antagonism of 5-HT<sub>2</sub> receptors. In addition, patients with SRI-resistant OCD may have additional abnormalities in dopaminergic function that require augmentation with dopamine-blocking agents. This review found a beneficial response to antipsychotic augmentation in about 50% of patients with SRI-resistant OCD.

**Glutamatergic agents.** Recent spectroscopy and animal studies have led to a third line of treatment for resistant OCD—glutamatergic agents. Dr. Pallanti explained that the rationale for this approach is based on a neuroimaging study that found abnormally high glutamatergic concentrations in the



caudate nuclei of untreated children with OCD.<sup>53</sup> Following SSRI treatment, a decrease in OCD symptom severity was associated with a decrease in caudate glutamatergic concentrations. Subsequently, medications with glutamatergic properties have been found effective in patients with resistant OCD. For example, Grant et al.<sup>54</sup> examined the efficacy of riluzole, a glutamate antagonist, in children with treatment-resistant OCD. The medication was well-tolerated and 4 of the 6 patients showed a decrease in symptoms following 12 weeks of open-label treatment.

Topiramate, an anticonvulsant with glutamatergic qualities, has shown efficacy as an adjunctive treatment in patients with resistant OCD.<sup>55,56</sup> Dr. Pallanti added that topiramate may be the first candidate in the glutamatergic line of treatment for resistant OCD; it enhances activity of  $\gamma$ -aminobutyric acid at nonbenzodiazepine sites, blocks voltage-gated sodium channels (which could decrease glutamate release), and is a weak inhibitor of carbonic anhydrase isoenzymes. Topiramate also has been shown to inhibit glutamate action via the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate subtype of glutamate receptors.

Augmentation with *N*-acetylcysteine (NAC), an amino acid compound, may be efficacious for treatment-resistant OCD. One case study<sup>57</sup> found that NAC was effective as adjunctive treatment with an SRI, but more studies of this agent are needed.

**Opioid agents.** Dr. Pallanti stated that another novel treatment strategy involves opioid antagonists. Results of an animal study<sup>58</sup> suggest a potential role of kappa opioid systems in hastening the pathogenesis of OCD and to the possibility that distinct brain regions may mediate the development and the expression of compulsive checking. Koran et al.<sup>59</sup> found that once-weekly oral morphine reduced median YBOCS scores in patients with treatment-resistant OCD by significantly more than placebo ( $p = .05$ ). However, the opioid antagonist naltrexone had no

significant effect on YBOCS scores when used adjunctively with SRIs.<sup>60</sup>

**Focal interventions.** If available pharmacologic treatments are ineffective, treatment-resistant patients may benefit from focal interventions. Dr. Pallanti identified 3 main types of focal interventions—transcranial magnetic stimulation (TMS), ablative stereotactic neurosurgery, and deep brain stimulation (DBS). He noted that research findings related to these treatments, although promising, should be considered experimental.

**Transcranial magnetic stimulation.** Dr. Pallanti explained that TMS is a noninvasive and painless neurophysiological technique that stimulates the brain. A large, brief current passes through a wire coil placed on the scalp and the transient current produces a large and changing magnetic field, which induces electric current in the brain.

Studies have evaluated the therapeutic effects of TMS in patients with OCD. Greenberg et al.<sup>61</sup> found that a single session of repetitive TMS (rTMS) of the right lateral prefrontal cortex produced a significant decrease in compulsive urges lasting 8 hours in patients with OCD ( $p < .02$ ). Mantovani et al.<sup>62</sup> examined the efficacy of 10 daily sessions of low-frequency rTMS in patients with OCD or Tourette's syndrome. In both groups, substantial symptom improvements had occurred by week 2, and patients were stable at the 3-month follow-up. Sachdev and colleagues<sup>63</sup> concluded from a 2-week study of daily treatment that about one quarter of treatment-resistant OCD patients responded to rTMS (of either the right or left prefrontal lobe), but this study had no sham treatment control group. A controlled study<sup>64</sup> measured the efficacy of low-frequency rTMS of the right prefrontal cortex and found no significant improvements in OCD symptoms compared with sham treatment. Further investigation of TMS is warranted, and intervention techniques (such as frequency and brain location) need perfecting.

**Ablative stereotactic neurosurgery.** Dr. Pallanti discussed 2 types of ablative stereotactic neurosurgery— anterior cingulotomy and anterior capsulotomy. Both procedures involve inserting probes through the skull (into the cingulum or the capsule). Then, small portions of tissue are burned away. The same surgery can also be done using external radiation.

Baer et al.<sup>65</sup> observed a 30% success rate following anterior cingulotomy in treatment-resistant OCD patients. A 24-month follow-up study of patients treated with the surgical procedure<sup>66</sup> found no significant side effects and a mean improvement of 48% on the YBOCS; 47% of the sample responded. Cosgrove and Rauch<sup>67</sup> advised that stereotactic cingulotomy be viewed as only part of a complete treatment plan.

Ruck et al.<sup>68</sup> assessed the long-term efficacy and safety of unilateral or bilateral capsulotomy in 25 patients with treatment-resistant OCD. At follow-up (mean = 10.9 years after surgery), 12 patients had achieved response and 9 were in remission. However, a high rate of adverse events was observed; only 3 patients achieved remission without experiencing adverse events.

**Deep brain stimulation.** Dr. Pallanti explained that DBS involves the insertion of a pacemaker-like device, which contains a battery and circuitry to generate electrical signals that are delivered to targeted structures deep within the brain. The clinician can program and adjust the settings of the neurostimulator externally via a handheld device.

Deep brain stimulation has advantages compared with traditional lesioning procedures, explained Dr. Pallanti. Specifically, the procedure is reversible, adjustable, and minimally invasive, and it has fewer side effects. However, the exact target of DBS in patients with OCD is still uncertain.<sup>69</sup>

## Conclusion

Dr. Pallanti concluded that treatment resistance occurs in many patients with OCD, and more research in

this area is needed. In the meantime, clinicians should use rating scales to assess patient responsiveness to treatment, to identify comorbid symptoms, and to measure QoL. Combination pharmacotherapy is the rule and not the exception in treatment-resistant OCD. Clinicians should consider the involvement of several neurotransmitters, not just serotonergic dysfunction, when devising a comprehensive treatment plan.

**Drug names:** citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), haloperidol (Haldol and others), lorazepam (Ativan and others), morphine (Kadian, Avinza, and others), naltrexone (Vivitol, Revia, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), riluzole (Rilutek and others), risperidone (Risperdal and others), sertraline (Zoloft and others), topiramate (Topamax).

**Disclosure of off-label usage:** The chair has determined that, to the best of his knowledge, desipramine, escitalopram, haloperidol, morphine, naltrexone, olanzapine, quetiapine, riluzole, risperidone, topiramate, and *N*-acetylcysteine are not approved by the U.S. Food and Drug Administration for the treatment of obsessive-compulsive disorder.

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