A Review of the Treatment for Refractory Obsessive-Compulsive Disorder: From Medicine to Deep Brain Stimulation

By David S. Husted, MD, and Nathan A. Shapira, MD, PhD

FOCUS POINTS

- Obsessive-compulsive disorder (OCD) is associated with extraordinary direct and indirect costs, with 30% to 40% of patients proving to be refractory to treatment.
- Based on clinical findings, associated disorders, and recent brain imaging studies, OCD appears to involve pathology of the orbitofrontal cortex, cingulate gyrus, and striatum.
- Serotonin is clearly an important neurochemical in OCD, possibly due to its ability to inhibit the seemingly hyperactive glutamatergic neurons of the orbitofrontal cortex.
- Selective serotonin reuptake inhibitors and atypical antipsychotics have been demonstrated to be effective pharmacologic agents in the treatment of OCD.
- A variety of stereotactic neurosurgical procedures have been shown to be effective and relatively safe for the treatment of severe, treatment-refractory OCD.

ABSTRACT

This article provides an overview of the etiology, epidemiology, and first-line treatment options for obsessive-compulsive disorder (OCD). The subject of treatment-resistant and treatment-refractory OCD is then discussed, including a definition of these often-debated terms, and the latest treatment options delineated. This includes a review of the latest research concerning the pharmacological agents that have been studied as monotherapy or augmenting agents for the treatment of OCD, the use of experimental medications and procedures, treatment with reversible, minimally invasive procedures, such as vagal nerve stimulation and transcranial magnetic stimulation, invasive but the potentially reversible deep brain stimulation, and irreversible lesioning with ablative psychosurgery. A discussion of the role of psychotherapy in the treatment of OCD is also included.

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INTRODUCTION

A review of the literature from 1970–2003 was conducted using MEDLINE, using the keywords "obsessive compulsive disorder and etiology," "obsessive compulsive disorder and epidemiology," "treatment of refractory obsessive compulsive disorder," "treatment of resistant obsessive compulsive disorder," "psychotherapy," and "obsessive compulsive disorder, deep brain stimulation and obsessive compulsive disorder," "vagal nerve stimulation and obsessive compulsive disorder," and "psychosurgery and obsessive compulsive disorder." The aims of this article include the description of obsessive-compulsive disorder (OCD) and its impact on society, the definition of the terms "refractory OCD" and "resistant OCD," recommendations of treatment algorithms based on the literature, and a discussion of novel procedures and medications for treating the refractory patient.

DESCRIPTION, EPIDEMIOLOGY, AND DIAGNOSIS OF OBSESSIVE-COMPULSIVE DISORDER

OCD is characterized by recurrent intrusive thoughts, images, or impulses (obsessions) that are typically ego-dystonic and anxiety producing. The obsessions commonly provoke the individual to engage in ritualistic behavior (compulsions) in an attempt to relieve the consequent anxiety. Compulsions are often governed by internal rules that

Dr. Husted is a third-year resident and Dr. Shapira is assistant professor, both in the Department of Psychiatry at the University of Florida College of Medicine in Gainesville, Florida.

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Please direct all correspondence to: David S. Husted, MD, Department of Psychiatry, University of Florida College of Medicine, P.O. Box 100256, Gainesville, FL 32610-0256. E-mail: dhusted@psychiatry.ufl.edu.

the affected individual feels must be applied rigidly and are not connected in a realistic way with the obsession they are designed to neutralize. They are often excessive and unreasonable, leading to marked impairment of the individual's social or occupational routine.

The symptoms of OCD are similar across the spectrum of cultures and have varied little in its description in the literature over the past century.[1] OCD is the fourth most prevalent psychiatric disorder in the United States, with a lifetime prevalence of 2.5%[2] and it has been estimated to affect ~% of the world's population.[3] Prevalence does not appear to differ across different ethnic backgrounds and populations. The male-to-female ratio of OCD is approximately equal, unlike the balance of anxiety disorders that are noted to be more common in females. OCD demonstrates a bimodal age of onset, with peaks prior to puberty and in the fourth decade of life.[4,5] A statistically significant association with pregnancy, miscarriage, or parturition has been reported,[5,6] as well as with streptococcal infections.[7] OCD has been noted to present with acute episodes (eg, sequelae of acute streptococcal infections in children [pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS)]), but more commonly is appreciated to be a chronic illness.[8]

Epidemiological studies[9] clearly demonstrate OCD to have a high comorbidity with other anxiety and mood disorders and an association with greater impulsivity and suicide attempts. Obsessive-compulsive symptoms are also noted to be inherent to other psychiatric disorders, including Tourette's syndrome, autism, body dysmorphic disorder, and hypochondriasis.[10] OCD is associated with extraordinary direct and indirect costs given the chronic nature of the illness, the strong desire by many patients to hide their pathology due to embarrassment with consequent delay in diagnosis and treatment, ignorance by the clinician with resultant underdiagnosis and inappropriate treatment, and the 30% to 40% of patients who prove refractory to treatment.[11,12] The severity of symptoms is best measured by using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS),[13] given the reliability and validity of this scale in a number of randomized controlled trials of OCD.[14] The scale is relatively easy to administer and has been adapted for use in children and adolescents.[15]

ETIOLOGY OF OBSESSIVE-COMPULSIVE DISORDER

Symptomatology of OCD is evident in a variety of disorders of the striatum, including Tourette's syndrome, Sydenham's chorea, Huntington's disorder, and Parkinson's disorder.[16] Therefore, it has been hypothesized that OCD involves pathology of the striatum and recent brain imaging[17] provides persuasive data to support this hypothesis. Structural imaging studies have demonstrated significantly decreased volume and increased grey matter density of the corticostriatal-thalamic-cortical circuits in the setting of OCD. Likewise, functional imaging studies[18,19] consistently demonstrate increased baseline activity in the orbitofrontal cortex, cingulate gyrus, and striatum in OCD patients, with markedly increased activity when their obsessions are exacerbated. Positron computed tomographic studies in patients with OCD symptoms have consistently shown increased [^{18}F]2-fluoro-2-deoxy-D-glucose uptake in the prefrontal cortex, substantiating the hypothesis that this region, among others, is hyperactive in OCD.[18] Other studies[19-21] have also indicated a role for the temporal region and the amygdala. Functional imaging studies[22] performed in patients following pharmacotherapy and behavioral therapy have demonstrated normalization of brain activity in the corticostriatal-thalamic-cortical circuitry. Tot and colleagues[23] demonstrated frontotemporal dysfunction on electroencephalograms (EEGs) of subjects with unmedicated OCD, further emphasizing the role this region of the brain plays in OCD.

Serotonin (5-HT) appears to be an important factor in the pathogenesis of OCD. It is postulated that OCD patients have, amongst other abnormalities, excessive baseline activity of the excitatory glutamatergic neurons of the orbitofrontal cortex. 5-HT is a known inhibitor of these neurons, which would lead one to postulate that increased release of 5-HT by the serotonergic neurons of the orbitofrontal cortex would lead to a diminution of symptoms clinically. Studies[24-28] indicate that the important 5-HT subreceptors in OCD appear to be the 5-HT_{2C} and 5-HT_{1D} receptors. Studies[29] demonstrate that desensitization of the 5-HT_{1D} receptor requires a high dose and long duration of administration of serotonin reuptake inhibitors (SRIs), which correlates with what is clinically observed to diminish the symptoms of OCD. Dopamine is another neurotransmitter of the cortico-striatal-thalamic-cortical system that appears important in the pathology of OCD. Administration of dopamine agonists in preclinical studies has been noted to exacerbate symptoms and tics of OCD.[30] Dopamine blockers, such as atypical antipsychotics, are the Food and Drug Administration-indicated treatment for Tourette's syndrome, which is considered part of the OCD spectrum. As discussed later, atypical antipsy-

chotics have been shown to be effective augmentation agents in treatment-refractory OCD.

The investigation of a potential autoimmune basis of OCD has been a focus of recent research. Over a decade ago, an association between OCD and Sydenham's chorea was confirmed, leading many to hypothesize the presence of an autoimmune disruption of cortico-striatal-thalamic-cortical circuits in at least a subpopulation of OCD patients.[31] In the past decade, a body of literature has described the possible existence PANDAS. This disease appears to be a syndrome in which children develop acute OCD symptomatology following a clinical or subclinical streptococcal infection.[7] Systematic studies[32] have demonstrated the onset and subsequent exacerbations of OCD and tics in this subset of children to be caused by group A β-hemolytic streptococcal (GABHS) infections. It appears the autoimmune reaction is mediated by autoantibody production, as studies demonstrate increased expression of D8/17, a β-lymphocyte antigen, and the presence of autoantibodies in affected patients. These antistreptococcal-antineuronal antibodies appear to target the basal ganglia and other central nervous system regions, leading to OCD symptomatology, dystonia, chorea, choreoathetosis, and encephalopathy.[33,34] Research has demonstrated a significant improvement in OCD symptoms following antibiotic treatment of acute exacerbations in PANDAS patients.[32] However, further studies are needed before antibiotic treatment in PANDAS patients can be considered the standard of care. Intravenous (IV) immunoglobulin and plasmapharesis are additional means of treating acute exacerbations in PANDAS patients that seem to be effective.[35]

DEFINITION OF RESISTANT AND REFRACTORY OBSESSIVE-COMPULSIVE DISORDER

Few patients with OCD ever experience complete resolution of symptoms. In fact, effectiveness of treatment is often gauged by the clinician as a decrease in symptoms to a level the patient finds tolerable and at which the patient is able to function. In clinical trials, a 25% to 35% reduction of mean Y-BOCS scores is considered an adequate response to a given treatment.[36] Even this modest reduction in Y-BOCS scores is not achieved in 40% to 60% of patients, though.[36] The terms "treatment-resistant" and "treatment-refractory" are often used interchangeably. The synonymous use of these terms is likely a relic of the past, in which the medication options for treating OCD were limited and resistance to first- and second-line treatment exhausted the available options. With the availability of modern treatment options, it is generally accepted that the failure of at least two adequate therapeutic trials of SRIs constitutes treatment-resistant OCD.[36] The term "treatment-refractory" denotes a greater degree of resistance, but it is still debatable at which point in treatment this term becomes applicable. Based on a review of the literature and our own clinical experience, it seems reasonable to consider patients who fail a number of therapeutic trials of SRIs, standard augmentation strategies, and behavioral therapy to be treatment-refractory. Patients who demonstrate some response to treatment yet still experience significant impairment from their residual OCD symptoms should also be considered to be treatment-refractory. This is the definition of treatment-refractory that is generally used for the selection of patients for novel treatments, psychosurgery, and deep brain stimulation. For the purpose of this review, therefore, treatment-refractory generally applies to patients who have failed at least three therapeutic trials of SRIs (with clomipramine being one of the SRI trials), the use of at least two atypical antipsychotics as augmenting agents, and treatment with behavioral therapy while on a therapeutic dose of an SRI. These patients have "failed" treatment by demonstrating <25% reduction of Y-BOCS scores or, despite >25% reduction in Y-BOCS score, by still experiencing significant impairment from their illness.

Prior to labeling a patient treatment-resistant or treatment-refractory, however, it is important for the clinician to re-evaluate the diagnosis, exclude comorbid diagnoses that could be contributing to overall poor function (eg, depression, psychosis, etc.), and confirm adequate treatment trials in the past. In addition, it is the rare patient who has been involved in an adequate trial of behavioral therapy, which means few patients truly can be considered to be treatment-refractory. Therefore, it is important for the clinician to insist on an adequate course of behavioral therapy prior to labeling the patient treatment-refractory and referring them for surgical treatment.

Goodman and colleagues[36] suggest the consideration of endpoint severity in the classification of patients as treatment responders versus partial responders. The authors argue that patients that demonstrate an improvement in Y-BOCS score to a level of minimal severity (Y-BOCS <16) should be considered full responders (responders) while those with endpoint Y-BOCS scores >19.5 (moderate severity) be considered partial responders. Therefore, patients with severe OCD (baseline Y-BOCS >30) that dem-

onstrate an adequate response to treatment (25% to 35% reduction in Y-BOCS score) would still be considered partial responders to the treatment regimen and, if that regimen consisted of multiple SRI trials, augmentation agents, and behavioral therapy, would also be considered treatment-refractory.

PHARMACOLOGIC STRATEGIES IN THE TREATMENT OF OBSESSIVE-COMPULSIVE DISORDER

SRIs, which include clomipramine and selective serotonin reuptake inhibitors (SSRIs), have been demonstrated in a number of rigorous randomized controlled studies to be effective in treating OCD in both adults and children.[37,38] Double-blind placebo controlled trials[39-42] have specifically demonstrated the efficacy of sertraline, fluoxetine, paroxetine, and fluvoxamine in the treatment of OCD. All of the SSRIs demonstrate better safety and tolerability profiles than the previous standard of treatment, clomipramine.[36,43] Geller and colleagues[43] demonstrated clomipramine to have greater efficacy than fluvoxamine, sertraline, paroxetine, and fluoxetine in a meta-analysis of 12 double-blind, placebo controlled studies involving 1,044 children and adolescents with OCD. While all of the SRIs studied showed significant efficacy, multivariate regression analysis of drug effect with other variables controlled demonstrated clomipramine to have significantly greater reduction in OCD symptoms versus the SSRIs (P=.002, χ^2test). The authors stopped short of recommending clomipramine as the first-line treatment in the pediatric population, however, given its greater side-effect profile and higher risk for adverse events.

Clinical experience supports the conclusion of research studies, which demonstrate a trial of SRIs for long duration (10–12 weeks) and high dose (often the maximum recommended dose) is often required for good efficacy in OCD.[44,45] Often in treating OCD, the clinician at best will experience only alleviation of symptoms, rather than complete remission. Even partial diminution of symptoms, though, can be associated with a significant improvement in quality of life and overall function.[46] In general, if the patient fails to demonstrate a significant response (≥25% reduction Y-BOCS) to an adequate trial of a particular agent, the clinician should switch treatment to a different SRI.[36,38] With a partial response, the clinician is best served to leave the initial agent in place and, assuming the given medication is already titrated to the maximum dose, add an additional agent to augment the effect.[36,38,46] Augmentation strategies largely consist of the use of atypical antipsychotics with or without behavioral therapy.[36,38,46]

Numerous studies document the strong relationship between tic disorders and OCD, with evidence of a greater than 35% prevalence of tic disorders in OCD patients.[47] Given antipsychotics are the standard treatment for Tourette's disorder, McDougle and colleagues[36] theorized that the concurrent use of neuroleptics and SRIs in the treatment of OCD patients with tics would be an effective regimen. In a double-blind, placebo-controlled trial, they demonstrated that haloperidol and fluvoxamine, when used in combination, led to significant improvement in Y-BOCS scores versus the use of fluvoxamine alone in these patients. Whereas the initial belief was that neuroleptic augmentation preferentially benefited OCD patients with comorbid tics, future research demonstrated OCD patients without evidence of tics also manifested significant improvement with antipsychotic augmentation.[36] This finding has led to a large body of research concerning the use of antipsychotics in treating OCD.

The literature to date demonstrates dopamine antagonists to be the most effective agent for augmentation, with the atypical antipsychotic agents being better tolerated than the traditional neuroleptics.[48] It is theorized that in addition to dopamine blockade, the synergistic action of blockade of 5-HT_{2A} receptors by atypical antipsychotics with the simultaneous inhibition of 5-HT uptake by SRIs leads to overall greater therapeutic efficacy.[49] McDougle and colleagues[50] demonstrated in a double-blind, placebo-controlled trial that risperidone augmentation at an average dose of 2.2 mg/day led to significant improvement in YBOCS scores versus that of an SRI plus placebo. Hollander and colleagues[51] and Arias and colleagues[52] demonstrated similar findings in double-blind placebo-controlled trials using risperidone to augment SRI treatment in treatment-resistant OCD patients. D'Amico and colleagues[53] reported efficacy with administration of olanzapine 10 mg/day as augmentation of paroxetine 60 mg/day in an open trial with 21 patients. Crocq and colleagues[54] reported similar findings in an open trial involving olanzapine augmentation of treatment resistant OCD. Bystritsky and colleagues[55] demonstrated in a double-blind, placebo-controlled study that a 6-week trial of olanzapine augmentation (5–20 mg/day, mean: 11.2 mg/day) of SRI treatment in refractory OCD led to significant improvement. However, in a double-blind, placebo-controlled trial, Shapira and colleagues[56] found no

demonstrated IV clomipramine to be effective in adults with OCD resistant to or intolerant of oral clomipramine and SSRIs in a double-blind, placebo-controlled trial. Pallanti and colleagues[86] administered IV citalopram in an open trial of 39 outpatients who had failed at least two trials of orally administered SRIs, excluding citalopram, and had moderate-to-severe OCD. After 21 days of IV citalopram, 59% of the trial subjects demonstrated at least a 25% decrease in Y-BOCS score. In a double-blind, pulse-loaded study involving IV clomipramine, Koran and colleagues[87] noted the subjects on IV clomipramine (n=7) demonstrated a more rapid response (decrease in Y-BOCS score by >25% by day 4.5) than those on oral clomipramine (n=8). There was no significant difference in change in Y-BOCS score, however, between the two study groups at the endpoint of the study (8 weeks). Further double-blind trials evaluating the efficacy of IV clomipramine are currently ongoing.

Inositol is a phospholipid that serves as a key metabolic precursor in G-protein-coupled receptors in the brain. Several subtypes of serotonergic, adrenergic, and glutamatergic receptors are coupled to phosportidylinositol (PI) hydrolysis. Myoinositol is vital to the resynthesis of PI and, therefore, the sustaining of second-messenger signaling at these receptors. Inositol has been found to be effective monotherapy in at least one double-blind, controlled crossover trial of OCD.[88] Thirteen OCD patients were randomized to either inositol 18 g/day or placebo for 6 weeks, with significantly lower Y-BOCS scores noted in the inositol group. Fux and colleagues[89] investigated the possible role of inositol as an augmenting agent to SRI treatment in OCD. Ten OCD patients were enrolled in a double-blind, randomized, crossover study with either inositol 18 g/day or placebo for 6 weeks in addition to their ongoing SRI treatment. No significant difference was found between the two groups. Inositol has been noted in other studies to be effective in treating panic disorder and major depressive disorder (MDD).[88] The efficacy of inositol in treating OCD, panic, and depression does not appear to be solely related to replenishing the pool of PI. Biochemical studies[90] have demonstrated the ability of inositol to alter receptor sensitivity, modulate an array of signaling proteins, and direct membrane trafficking.

The role of the endogenous opioid system in the pathophysiology of OCD has been postulated by a number of researchers, given some evidence in the literature that opioid antagonists exacerbate OCD symptoms.[91] The use of the opioid agonist tramadol hydrochloride as monotherapy for OCD has, therefore, been investigated in at least one open-label study. Shapira and colleagues[91] enrolled seven patients with OCD nonresponsive to treatment with at least one therapeutic trial of an SRI, and six subjects completed a 6-week period of treatment with tramadol at an average dose of 254 mg/say. The average Y-BOCS score was noted to decrease by 26% over that time period ($z=2$, $df=1$, $P<.05$), leading the researchers to conclude tramadol is a potentially useful alternative medication for treatment-resistant OCD. Koran and colleagues[92] performed a double-blind, placebo-controlled trial investigating the benefit of oral morphine in treatment-resistant OCD. Subjects enrolled in the study carried a diagnosis of OCD for >3 years, had failed an average of 3.4 previous SRI trials, and had a Y-BOCS score of >21 (median Y-BOCS: 28). All of the 19 study subjects were administered oral morphine sulfate 15–45 mg/day, oral lorazepam 0.5–1 mg/day, and placebo in random order in 2-week blocks. Concurrent medications (13 subjects on SRIs, one subject on benzodiazepines alone, one subject on buproprion alone) were maintained throughout the study. Six study subjects were noted to demonstrate a significant decrease in Y-BOCS score when treated with morphine (median Y-BOCS: 17, median decrease: 41%). Koran and colleagues[25] theorized that opiates decrease OCD symptoms via inhibition of glutamate release in the cerebral cortex, disinhibition of serotonergic neurons in the dorsal raphe,[93] and increased dopamine transmission in the striatum.[94]

Mirtazapine is a novel antidepressant that blocks presynaptic α-2 adrenergic receptors and postsynaptic 5-HT_2 and 5-HT_3 receptors, leading to an increase in central norepinephrine and 5-HT. Due to the increase in 5-HT levels, it is expected that patients with OCD would manifest improvement following treatment with mirtazapine. Koran and colleagues[95] enrolled 10 patients in an open-label, 10-week trial of mirtazapine as monotherapy. No significant improvement in Y-BOCS scores was appreciated, although only 6 patients completed the study, and doses higher than >45 mg of mirtazapine were not utilized. For this reason, Koran and colleagues[96] performed a follow-up study that involved 15 treatment-naïve patients (mean Y-BOCS score of 27.8, diagnosed with OCD >1 year) treated with mirtazapine (mean dose: 54 mg/day) in a 12-week open-label trial. Eight patients were responders (Y-BOCS decrease >25% and CGI-I "much improved" or "very much improved"), and

were then randomized to placebo or mirtazapine in an 8-week double-blind, continuation/discontinuation study. To date, the blind has not been broken in the second phase of the study and, therefore, conclusions have yet to be drawn concerning the efficacy of mirtazapine in OCD.

Treatment for OCD typically requires lifelong medication administration, as symptoms of OCD rarely abate over time untreated. Further, some data indicates reinstatement of a medication following relapse can be associated with a poorer response than was seen with initial use.[97] Therefore, it is the unusual situation in which the clinician will feel it is indicated to taper a patient's medication to off.

PSYCHOTHERAPY FOR TREATMENT OF OBSESSIVE-COMPULSIVE DISORDER

Psychotherapy is an important component of treatment for OCD that is, tragically, underutilized by the clinician. In his writings, Freud devoted a fair amount of attention to OCD, postulating that OCD existed on a spectrum ranging from obsessive-compulsive personality disorder to psychosis. Psychoanalytic treatment was suggested by Freud[98] and was the accepted treatment for OCD for half a century.[1] At present, it appears there is little data to support such an approach. Behavioral therapy is the current focus of psychotherapy in the treatment of OCD. In treating OCD, behavioral therapy consists largely of exposure to feared stimuli and the prevention of a subsequent response. The therapist prompts the patient to make a hierarchal list of their obsessions and compulsions, which is arranged in order from the least anxiety-provoking symptoms to the most anxiety-provoking. The patient is then repeatedly exposed to the provocative stimuli and their typical compulsive response is discouraged. This continues until the stimulus is no longer anxiety-provoking, upon which the therapist moves on to the next stimulus in the hierarchy. At least 25% of OCD patients are unable to tolerate behavioral therapy, though, due to the stress of being exposed to feared stimuli, while 20% to 30% demonstrate little or no improvement.[99]

A number of controlled studies[100,101] demonstrate significant improvement in OCD with concurrent behavioral therapy and SSRI treatment, and two meta-analyses[102,103] found no differences between the two approaches when used separately. Another meta-analysis appears to demonstrate a superior outcome with behavioral therapy alone versus that of SSRI treatment.[104] Individuals with OCD treated with therapy have been found to maintain their gains following discontinuation of treatment, while up to 80% of patients treated pharmacologically relapse upon treatment discontinuation.[105] With the exception of Albert and colleages[106] though, no well designed study to date has demonstrated an improvement in Y-BOCS scores using behavioral therapy in patients partially responsive to SRI monotherapy. While an argument can be made for the use of behavioral therapy in addition to pharmacotherapy, the literature to date provides insufficient evidence to guide clinical practice.[105] However, leading experts[44,45] in OCD generally agree that behavioral therapy should be incorporated into the treatment plan when SRI monotherapy is inadequate. Thus, psychotherapy is an important method of augmentation if it is available and can be tolerated and afforded by the patient, and is as effective—if not more effective—for monotherapy as SRIs in treating OCD.

Whereas the principle component of behavioral therapy is exposure to feared stimuli and response prevention, cognitive therapy focuses on insight into the overestimation of threat, the excessive concern about controlling thoughts, and the over importance of thoughts found in OCD. The cognitive theory of OCD proposes that obsessional thoughts and normal intrusive thoughts differ on how the patient interprets the occurrence and content of the intrusions.[101] Obsessional patients interpret intrusive cognitions as an indication that they may be responsible for prevention of harm to themselves or another, leading to the feeling of discomfort and the overt or covert neutralizing behaviors. Cognitive therapy seeks to eliminate responsibility beliefs, relieving discomfort and minimizing the perceived need to engage in neutralizing rituals. Cognitive therapy is theoretically beneficial in the OCD patient who is unable to comply with exposure therapy with response prevention. A meta-analysis of 15 published studies of cognitive therapy in OCD[107] found no significant benefit, though. Cognitive therapy may, therefore, be used for treating OCD if behavioral therapy fails or is poorly tolerated, but the literature currently lends little support to it being efficacious.

The cost of the many treatment sessions needed and the lack of experienced therapists can be prohibitive for the use of psychotherapy in the treatment of OCD. Group therapy is one manner in which OCD patients could undergo therapy with a proven therapist at a less prohibitive cost. Recent studies[108,109] have demonstrated the efficacy of group therapy in OCD. However, group therapy may not be as beneficial as individual therapy in severely ill OCD patients, and may lead to less improvement in Y-BOCS scores in the average OCD patient.

In using psychotherapy to treat OCD, it is quite important to involve the patient's family members, significant others, and friends, as the symptoms of OCD often greatly affect (and involve) those close to the patient.[101] Involvement of family members in therapy will help alert those who serve as enablers for the patient's compulsive behavior, and through facilitating this awareness, assist the patient in refraining from this behavior.

NEUROSURGERY FOR TREATMENT-REFRACTORY OBSESSIVE-COMPULSIVE DISORDER

Ablative neurosurgery (psychosurgery) has been practiced for decades for a variety of debilitating psychiatric conditions, including schizophrenia, bipolar disorder, and OCD. As the pharmacologic treatment of these conditions have improved in efficacy and side-effect profile, the role of psychosurgery has diminished. However, in the setting of OCD, a condition that can be markedly impairing and commonly unresponsive to a variety of treatment regimens, psychosurgery has remained a viable option. Patients with refractory OCD typically have insight into their condition and are desperate for relief from their symptoms, which makes the risks of surgery acceptable. A variety of stereotactic neurosurgical procedures have been described in the literature for treatment of severe, treatment-refractory OCD. In general, these procedures involve radiofrequency ablation of a portion of the corticostriatal circuit, which consists of the orbitofrontal cortex, the caudate nucleus, the pallidum, the thalamus, and the anterior cingulate cortex.[110,111] The anterior cingulate cortex directly communicates with the posterior cingulate cortex via projections through the cingulum, and is closely related to the orbitofrontal cortex and the caudate nucleus.[112] The main regions of pathogenesis of OCD are believed to be the orbitofrontal cortex, cingulated gyrus, basal forebrain, and the caudate nucleus.[113,114] Differences between the various procedures mainly involve the location of the lesion and side-effect profile postoperatively. Anterior cingulotomy specifically targets the anterior cingulate cortex and the fibers of the cingulum, while anterior capsulotomy and subcaudate tracheotomy interrupts the frontothalamic fibers (basal forebrain).[115,116] Limbic leukotomy, which combines anterior cingulotomy and lesioning of the frontothalamic projections, was first described by Kelly and colleagues[117] and is often performed in a staged manner. To date, no trial has been performed to compare the efficacy of limbic leukotomy to that of anterior cingulotomy alone.

The mechanisms by which psychosurgery improves OCD symptomatology is to date poorly understood. A recent morphometric magnetic resonance imaging (MRI) study[118] demonstrated a reduction in volume of the posterior cingulate cortex following anterior cingulotomy, while a report of bilateral orbitomedial leukotomy showed persistently reduced metabolism in the cingulate gyrus following surgery.[119] The literature, therefore, suggests persistent metabolic changes of the anterior and posterior cingulate gyrus after lesioning the anterior cingulate, which may be the mechanism by which OCD symptoms improve following surgery. There appears to be a delay in onset of symptom improvement, suggesting the benefit of surgery is related not only to interruption of neural pathways, but also the reorganization of neural pathways following surgery.[120] This correlates well with the clinical finding of continuous improvement in OCD symptoms for >1 year postoperatively.[121] The different psychosurgical procedures for OCD are roughly comparable in efficacy, and appear to be relatively safe with low risk for long-term adverse effects.[120-122] Given the anterior cingulated cortex is closely approximated to the fronto-striato-pallido-thalamo-frontal circuit, one could expect the potential for postoperative frontal lobe abnormality and executive dysfunction.[110,111] Both the anterior cingulate gyrus and the substantia innominata are thought to be critical to the conversion of motivation into action.[123] Therefore, lesions can present clinically as apathy or affective blunting. The anterior cingulated gyrus is also involved in visceromotor control mechanisms, including bowel and bladder evacuation.[124] The risk of incontinence postoperatively is consequently not surprising. The role of the cingulate cortex in learning and memory is also established in the literature,[125] and lesioning of this region can impair this function. Reports of transient memory deficits and cognitive function impairments[122] have been noted in the literature, although the incidence is rare and the changes noted are quite subtle. Most studies of cognitive function[126] have, in fact, demonstrated no significant deficits following cingulotomy.

ANTERIOR CINGULOTOMY

Kim and colleagues[127] reported a prospective investigation of the efficacy of stereotactic bilateral anterior cingulotomy in 14 patients with severe, treatment-refractory OCD. The authors defined treatment-refractory as being the administration of at least three SRIs—one of which must have been clomipramine—at maximal doses for >24 weeks with

at least 15 sessions of concurrent behavioral therapy. All patients had severe symptomatology of OCD, with marked impairment in socio-occupational function and a mean Y-BOCS score of 35. Significant improvement in OCD symptoms following anterior cingulotomy was appreciated in the study, with a mean decrease in Y-BOCS scores of 12.6 and a mean CGI-Improvement of 1.9 at 12 months follow-up (P=.001). The study demonstrated 43% of the subjects responded to anterior cingulotomy (CGI-I scores of "much" or "very much" improved), with no significant long-term adverse effects of surgery. Cognitive function was unimpaired postoperatively, with actual improvement in the Wisconsin Card Sorting Test (WCST) noted. Postoperative headaches, insomnia, and memory dysfunction was reported initially, but all adverse effects resolved within three months of surgery. Dougherty and colleagues,[121] Spangler and colleagues,[128] Baer and colleagues,[122] and Jenike and colleagues[129] have all published previous data demonstrating similar efficacy with anterior cingulotomy, although not all of these studies used MRI validation of lesion locations and modern diagnostic criteria for OCD. Using statistical parametric mapping of pre-operative cerebral metabolism with F-18-fluorodeoxyglucose positron emission tomography, Rauch and colleagues[130] demonstrated higher metabolic rates within the right posterior cingulate cortex in patients who subsequently responded to psychosurgery, suggesting that preoperative F-18-fluorodeoxyglucose positron emission tomography scanning could provide a means for determining good psychosurgical candidates.

LIMBIC LEUKOTOMY

Montoya and colleagues[131] described a retrospective chart review of 21 patients with either MDD or OCD who underwent limbic leukotomy using MRI-guided stereotactic technique. Patients with OCD were only eligible for study participation if they exhibited severe symptoms with profound impairment, and had failed conventional pharmacotherapeutic agents and cognitive-behavioral therapy (CBT). The mean duration of illness for these patients was 23.9 years and the average number of psychotropics used was 24 years. Eighteen patients with OCD underwent limbic leukotomy, with 12 patients having previously undergone bilateral anterior cingulotomy. Therefore, these 12 required only lesioning of the frontothalamic fibers (in essence, a "staged" limbic leukotomy), while the remaining 6 patients underwent concurrent anterior cingulotomy and lesioning of the frontothalamic fibers. At 26-month follow-up, physician-rated CGI scores demonstrated 42% of the patients were "responders," while self-rated CGI scores demonstrated 62% of the patients assessed themselves as "much improved" or "very much improved." Postoperative Y-BOCS values demonstrated a 36% "response" rate when compared with pre-operative Y-BOCS scores. Post hoc analysis demonstrated postoperative CGI scale scores to be significantly worse for patients who underwent a single procedure compared with those who underwent a staged limbic leukotomy, lending weight to the rationale of performing this procedure in a staged manner. Minor postoperative symptoms of headache, low-grade fever, and nausea/vomiting were commonly reported, but noted to last <48 hours. Somnolence and apathy was appreciated in a significant portion of patients, but was noted to be transient in nature. Persistent complex partial seizures, short-term memory problems, and incontinence were reported in at least 5% of the patients, though. Hay and colleagues[132] reported even greater efficacy (62% rated as responders) with limbic leukotomy in a cohort of 17 patients with severe OCD, although the authors used liberal criteria for improvement. Kim and colleagues[133] reported a retrospective review of the outcome of limbic leukotomy in 12 patients with severe OCD (mean Y-BOCS: 34). All 12 patients were noted to have marked social and occupational impairment, with consequent inability to function or work. Postoperatively, the mean Y-BOCS score was noted to be 3, and these results were appreciated to persist for the mean 45 months of postoperative follow-up. No significant morbidity was appreciated, except for one case of mild transient urinary incontinence.

VAGUS NERVE STIMULATION

Vagus nerve stimulation (VNS) is predicated on the belief that the tenth cranial nerve has reciprocal influences on the limbic system and higher cortical activity due to it being predominantly an afferent nerve, its extensive arborization within the brain, and its widespread distribution in the body. The vagus cell bodies convey information centrally to the nucleus tractus solitarius which then projects to the remainder of the brain via three pathways: an autonomic feedback loop; direct projections to the medullary reticular formation; and ascending projections to the forebrain. The ascending projections have connections to the locus coeruleus, parabrachial nucleus, thalamus, hypothalamus, amygdala, and stria terminalis: all regions involved in the modulation of mood and anxiety disorders.[134,135] VNS involves stimulation of the left vagus nerve in the cervical region using a bipolar pulse generator. This generator is implanted in the left chest wall and delivers electrical signals to the electrode that is wrapped

patients, three demonstrated a significant postoperative decrease in Y-BOCS scores (>35% decrease) during stimulator-on conditions. Furthermore, psychiatrist-rated stimulator-on Y-BOCS scores were significantly lower (19.8±8.0) than those during stimulator-off conditions (32.3±3.9), a result which was sustained for the >21 months of postoperative follow-up. The fourth patient was noted to have malfunctioning batteries that ultimately necessitated removal of the implant and classic bilateral anterior capsulotomy. One patient was noted to have immense disgust when confronted with fatty or oily substances. Following placement of the DBS electrode and with the stimulator-on condition, he was able to dip his finger in a vat of butter, taste it, and shake hands with the examiner who had smeared grease all over his hands in front of the patient. When the stimulator was switched off, the patient immediately requested help in washing his hands. Of note, preliminary data seemed to indicate a role for DBS in the treatment of depression, as a number of patients with co-morbid depression noted a marked improvement in mood with relapse during stimulator-off conditions.[143]

DBS is attractive from a research perspective as it allows for randomized, blinded research due to the reversible nature of the electrical stimulation. Intracerebral hemorrhage is the most serious adverse outcome from surgery.[135] Confusion, speech disturbance, parasthesia, oculomotor abnormalities, and muscle contractions are the most common complications of stimulation, although they are often transient and not generally disturbing to the patient.[136]

TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) is the least invasive form of physical treatment of OCD. This procedure, first introduced by Barker[144] in 1985, involves the induction of a magnetic field over the scalp by passing an electric current through a coil. The resultant electrical field causes depolarization of the cortex of the brain that leads to either net stimulation or disruption of the neurons in the given brain region. Repeated application of TMS to a given region is termed repetitive TMS (rTMS), and the repetitive use of frequencies greater than 1 Hz is termed fast-frequency rTMS (FF-rTMS). Most studies of TMS in the treatment of OCD use FF-rTMS. Greenberg and colleagues[145] evaluated 12 patients with OCD after a single session of right prefrontal rTMS, and noted no significant effect on obsessions. Greenberg did note, however, that the single session of rTMS resulted in a significant decrease in compulsive behavior that was sustained for ≥8 hours. Alonso and colleagues[146] performed real or sham rTMS on 18 patients with OCD, and found no significant change in Y-BOCS scores in either group following 18 20-minute sessions. Alonso and colleagues[146] utilized a large coil and a frequency of only one Hertz, however, which is a technique that differs from that which is used in most other rTMS studies. In performing quantitative analysis on the pooled data from two randomized-controlled trials of rTMS in treating OCD, Martin and colleagues[147] found no significant benefit from rTMS and sham TMS. However, the authors concluded that there was insufficient data to definitively evaluate the role of rTMS in treating OCD. Furthermore, the studies[144-147] used in the pooled analysis used different rTMS techniques and, arguably, were not appropriate to be pooled.

TMS is largely deemed to be a relatively safe procedure, with any adverse effects mainly related to the intensity and frequency of stimuli applied. FF-rTMS, therefore, carries the greatest risk of morbidity, with the most likely being a severe headache, a temporary shift in auditory threshold and, rarely, seizures.[141,148,149] The apparent ineffectiveness of rTMS in treating OCD may be related to the range of the magnet being inadequate to reach the central nervous system regions implicated in OCD. Given the encouraging results thus far with the use of TMS in depression, further evaluation of its efficacy in treating OCD appears warranted.

ELECTROCONVULSIVE THERAPY IN TREATING OBSESSIVE-COMPULSIVE DISORDER

No definitive trials have demonstrated the efficacy of electroconvulsive therapy (ECT) in treating OCD. There are a number of case reports[150] in the literature, however, that document some decline in OCD symptoms post-ECT. Most of the patients reported, though, had comorbid depression that also improved post-ECT. Thus, given the likelihood that their OCD symptoms were exacerbated by a mood disorder, it may be concluded that the noted improvement in OCD was secondary to resolution of depression. To date, expert consensus deems ECT to be not indicated in the treatment of OCD, unless it is being utilized to treat comorbid depression.[36,44]

CONCLUSION

OCD is a disorder characterized by recurrent intrusive ego-dystonic thoughts, images, or impulses (obsessions) that tend to provoke compulsive behavior in an attempt to relieve the anxiety. OCD affects ~3% of the population of the US, and has a similar prevalence worldwide. The association of other disorders of the striatum with OCD, as well as the results of recent brain imaging studies, suggest that OCD is related to striatal pathology. Abnormalities of the orbitofrontal cortex

and cingulate gyrus are also thought to be involved in OCD. The results of recent research strongly suggest a familial component to OCD. Genetic polymorphisms of certain serotonin receptor subtypes may play a role in the pathogenesis of OCD. Animal models and clinical research also suggest a role for serotonergic, glutamatergic, and possibly dopaminergic systems in OCD. As a result, SRIs and antipsychotics have become the mainstay of pharmacologic treatment.

Behavioral psychotherapy has also been shown to be effective in treating OCD, while the role of cognitive therapy in treating OCD is less well defined. A variety of stereotactic neurosurgical procedures have been described in the literature for the treatment of severe, treatment-refractory OCD. The different psychosurgical procedures for OCD are roughly comparable in efficacy, and appear to be relatively safe with low risk for long-term adverse effects. DBS, which is currently an accepted treatment for movement disorders such as Parkinson's disease, is a potentially promising alternative to traditional psychosurgery for the treatment of severe, treatment-refractory OCD. VNS and TMS aslo are less-invasive procedures that may also have a role in the treatment of OCD. CNS

REFERENCES

1. Stein DJ, Stone MH. *Essential Papers on Obsessive-Compulsive Disorders*. New York, NY: New York University Press; 1997.
2. Karno M, Goldin JM, Sorenson SB, et al. The epidemiology of obsessive compulsive disorder in five US communities. *Arch Gen Psychiatry*. 1988;45:1094-1099.
3. Bebbington PE. Epidemiology of obsessive-compulsive disorder. *Br J Psychiatry*. 1998;35(suppl):2-6.
4. Eichstedt JA, Arnold SL. Childhood-onset obsessive-compulsive disorder: a tic-related subtype of OCD? *Clin Psychol Rev*. 2001;21:137-157.
5. Geller PA, Klier CM, Neugebauer R. Anxiety disorders following miscarriage. *J Clin Psychiatry*. 2001;62:432-438.
6. Williams KE, Koran LM. Obsessive-compulsive disorder in pregnancy, the puerperium, and the premenstruum. *J Clin Psychiatry*. 1997;58:330-334.
7. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry*. 1998;155:264-271.
8. Skoog G, Skoog I. A 40-year follow-up of patients with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1999;56:121-127.
9. Hollander E, Greenwald S, Neville D, Johnson J, Homig CD, Weissman MM. Uncomplicated and comorbid obsessive-compulsive disorder in an epidemiologic sample. *Depress Anxiety*. 1997;4:111-119.
10. Hollander E. *Obsessive-Compulsive Related Disorders*. Washington, DC: American Psychiatric Press; 1993.
11. Dupont RL, Rice DP, Shiraki S, et al. Economic costs of obsessive-compulsive disorder. *Med Interface*. 1995;8:102-109.
12. Newth S, Rachman S. The concealment of obsessions. *Behav Res Ther*. 2001;39:457-464.
13. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown obsessive compulsive scale. I: development, use, and reliability. *Arch Gen Psychiatry*. 1989;46:1006-1011.
14. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown obsessive compulsive scale. II: validity. *Arch Gen Psychiatry*. 1989;46:1012-1016.
15. Scahill L, Riddle MA, McSwiggin-Hardin M, et al. Children's Yale-Brown obsessive compulsive scale: reliability and validity. *J Am Acad Child Adolesc Psychiatry*. 1997;36:844-852.
16. Stein DJ, Hollander E, and Cohen L. Neuropsychiatry of obsessive-compulsive disorder. In: Hollander E, Zohar J, Marazziti D, Olivier B, eds. *Current Insights in Obsessive-Compulsive Disorder*. Chicester, UK: Wiley; 1994:167-182.
17. Rauch SL, Baxter LR Jr. Neuroimaging in obsessive-compulsive disorder and related disorders. In: Jenicke MA, Baer L, Minichiello WE, eds. *Obsessive-Compulsive Disorders: Practical Management*. 3rd ed. St Louis, Mo: Mosby; 1998:289-317.
18. Rosenberg DR, Keshavan MS. Toward a neurodevelopmental model of obsessive-compulsive disorder. *Biol Psychiatry*. 1998;43:623-640.
19. Hugo F, van Heerden BB, Zungu-Dirwayi N, Stein DJ. Functional brain imaging in obsessive-compulsive disorder secondary to neurological lesions. *Depress Anxiety*. 1999;10:129-136.
20. Zungu-Dirwayi N, Hugo F, van Heerden BB, Stein DJ. Are musical obsessions a temporal lobe phenomenon? *J Neuropsychiatry Clin Neurosci*. 1999;11:398-400.
21. Szeszko PR, Robinson D, Alvir JMJ, et al. Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1999;56:913-19.
22. Baxter LR, Schwartz JM, Bergman KS, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for OCD. *Arch Gen Psychiatry*. 1992;49:681-689.
23. Tot S, Ozge A, Comelekoglu U, et al. Association of QEEG findings with clinical characteristics of OCD: evidence of left frontotemporal dysfunction. *Can J Psychiatry*. 2002;47:538-545.
24. Bergqvist PB, Dong J, Blier P. Effect of atypical antipsychotic drugs on 5-HT2 receptors in the rat orbito-frontal cortex: an in vivo electrophysiological study. *Psychopharmacology*. 1999;143:89-96.
25. Koran LM, Pallanti S, Quercioli L. Sumatriptan, 5-HT(1D) receptors and obsessive-compulsive disorder. *Eur Neuropsychopharmacol*. 2001;11:169-172.
26. Stein L, Zohar J, Cohen R, Sasson Y. Treatment of severe, drug resistant obsessive compulsive disorder with the 5-HT(1D) agonist sumatriptan. *Eur Neuropsychopharmacol*. 1998;8:325-328.
27. Mundo E, Richter MA, Sam F, Macciardi F, Kennedy JL. Is the 5-HT(1Dbeta) receptor gene implicated in the pathogenesis of obsessive-compulsive disorder? *Am J Psychiatry*. 2000;157:1160-1161.
28. Stein DJ, van Heerden BB, Wessels CJ, et al. Single photon emission computed tomography of the brain with tc-99m HMPAO during sumatriptan challenge in obsessive-compulsive disorder: investigating the functional role of the serotonin auto-receptor. *Prog Neuropsychopharm Biol Psychiatry*. 1999;23:1079-1099.
29. El Mansari M, Bouchard C, Blier P. Alteration of serotonin release in the guinea pig orbito-frontal cortex by selective serotonin reuptake inhibitors. *Neuropsychopharmacology*. 1995;13:117-127.
30. Goodman WK, McDougle CJ, Lawrence LP. Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive-compulsive disorder. *J Clin Psychiatry*. 1990;51(suppl):36-43.
31. Swedo SE, Rapaport JL, Cheslow DL, et al. High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. *Am J Psychiatry*. 1989;146:246-249.
32. Leonard HL, Swedo SE. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). *Int J Neuropsychopharmacol*. 2001;4:191-198.
33. Eisen JL, Leonard HL, Swedo SE, et al. The use of antibody D8/17 to identify B cells in adults with obsessive-compulsive disorder. *Psychiatry Res*. 2001;104:221-225.
34. Stein DJ, Goodman WK, Rauch SL. The cognitive-affective neuroscience of obsessive-compulsive disorder. *Curr Psychiatry Rep*. 2000;2:341-346.
35. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorder in childhood. *Lancet*. 1999;354:1153-1158.
36. Goodman WK, Ward HE, Kablinger AS, Murphy TK. Biological approaches to treatment-resistant obsessive-compulsive disorder. In: Goodman WK, Rudorfer MV, and Maser JD, eds. *Obsessive-Compulsive Disorder: Contemporary Issues in Management*. London, UK: Lawrence Erlbaum Associates; 2000:333-369.
37. Grados MA, Riddle MA. Pharmacological treatment of childhood obsessive-compulsive disorder: from theory to practice. *J Clin Child Psychol*. 2001;30:67-79.

38. Dougherty DD, Rauch SL, Jenike MA. Pharmacological treatments for obsessive compulsive disorder. In: Nathan PE, Gorman JM, eds. *A Guide to Treatments That Work*. 2nd ed. London, UK: Oxford University Press; 2002:387-410.
39. Greist J, Chouinard G, DuBoff E, et al. Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1995;52:289-295.
40. Tollefson G, Birkett M, Kolman L, Genduso L. Continuation treatment of OCD: double-blind and open-label experience with fluoxetine. *J Clin Psychiatry*. 1994;55:69-78.
41. Wheadon DE, Bushnell WD, Steiner M. A fixed-dose comparison of 20, 40, or 60 mg paroxetine to placebo in the treatment of OCD. Paper presented at: Annual Meeting of the American College of Neuropsychopharmacology; December 7-11, 1993; Honolulu, Hawaii.
42. Goodman WK, Price LH, Rasmussen SA, et al. Efficacy of fluvoxamine in obsessive-compulsive disorder. A double-blind comparison of fluvoxamine and placebo. *Arch Gen Psychiatry*. 1989;46:36-40.
43. Geller DA, Biederman J, Stewart SE, et al. Which SSRI? A meta-analysis of pharmacotherapy in pediatric obsessive-compulsive disorder. *Am J Psychiatry*. 2003;160:1919-1928.
44. March JS, Frances A, Carpenter D, Kahn D. Treatment of obsessive-compulsive disorder: The Expert Consensus Panel for obsessive-compulsive disorder. *J Clin Psychiatry*. 1997;58(suppl):1-72.
45. American Academy of Child and Adolescent Psychiatry. Practice parameters for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 1998;37(suppl):27-45.
46. Ballenger JC. Treatment of anxiety disorders to remission. *J Clin Psychiatry*. 2001;62(suppl):5-9.
47. McDougle CJ, Goodman WK, Leckman JF, et al. Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder: a double-blind, placebo-controlled study in patients with and without tics. *Arch Gen Psychiatry*. 1994;51:302-308.
48. Albert U, Bergesio C, Pessina E, et al. Management of treatment resistant obsessive-compulsive disorder: algorithms for pharmacotherapy. *Panminerva Med*. 2002;44:83-91.
49. Marek GJ, Carpenter LL, McDougle CJ, Price LH. Synergistic action of 5-HT2A antagonists and selective serotonin reuptake inhibitors in neuropsychiatric disorders. *Neuropsychopharmacology*. 2003;28:402-412.
50. McDougle CJ, Epperson CN, Pelton GH, et al. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2000;57:794-802.
51. Hollander E, Ross NB, Sood E, Pallanti S. Risperidone augmentation in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo controlled study. *Int J Neuropsychopharmacol*. 2003;6:397-401.
52. Arias F, Soto JA, Garcia MJ, et al. Efficacy and tolerance of risperidone addition in serotonin reuptake inhibitors (SRI) treatment for refractory obsessive-compulsive disorder. *Eur Neuropsychopharmacol*. 2002;12(suppl 3):S341.
53. D'Amico G, Cedro C, Muscatello MR, et al. Olanzapine augmentation of paroxetine-refractory obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27:619-623.
54. Crocq MA, Leclercq P, Guillon MS, Bailey PE. Open-label olanzapine in obsessive-compulsive disorder refractory to antidepressant treatment. *Eur Psychiatry*. 2002;17:296-297.
55. Bystritsky A, Ackerman DL, Rosen RM, et al. Augmentation of SSRI response in refractory OCD using adjunct olanzapine: a placebo-controlled trial. APA Annual Meeting, New Research Abstracts; 2001; New Orleans, LA:171-172.
56. Shapira NA, Ward HE, Mandoki M, et al. Placebo-controlled trial of fluoxetine versus fluoxetine plus olanzapine in obsessive-compulsive disorder. Paper presented at: Annual Meeting of the New Clinical Drug Evaluation Unit; May 29, 2003; Boca Raton, FL.
57. Denys D, Van Megen H, Westenberg HGM. Quetiapine addition to serotonin reuptake inhibitor treatment in patients with treatment-refractory obsessive-compulsive disorder: an open-label study. *J Clin Psychiatry*. 2002;63:700-702.
58. Atmaca M, Kuloglu M, Tezcan E, Gecici O. Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. *Int Clin Psychopharmacol*. 2002;17:115-119.
59. McDougle CJ, Barr LC, Goodman WK, et al. Lack of efficacy of clozapine monotherapy in refractory obsessive-compulsive disorder. *Am J Psychiatry*. 1995;152:1812-1814.
60. Lykouras L, Alevizos B, Michalopoulou P, Rabavilas A. Obsessive-compulsive symptoms induced by atypical antipsychotics: a review of the reported cases. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27:333-346.
61. de Haan L, Beuk N, Hoogenboom B, et al. Obsessive-compulsive symptoms during treatment with olanzapine and risperidone: a prospective study of 113 patients with recent-onset schizophrenia or related disorders. *J Clin Psychiatry*. 2002;63:104-107.
62. Jenike MA, Baer L, Minichiello WE, et al. Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. *Am J Psychiatry*. 1997;154:1261-1264.
63. Pigott TA, Pato MT, L'Heureux F, et al. A controlled comparison of adjuvant lithium carbonate or thyroid hormone in clomipramine-treated patients with obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1991;11:242-248.
64. McDougle CJ, Price LH, Goodman WK, et al. A controlled trial of lithium augmentation in fluvoxamine-refractory obsessive compulsive disorder: lack of efficacy. *J Clin Psychopharmacol*. 1991;11:175-184.
65. Pigott TA, L'Heureux F, Hill JL, et al. A double-blind study of adjuvant buspirone hydrochloride in clomipramine-treated patients with obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1992;12:11-18.
66. McDougle CJ, Goodman WK, Leckman JF, et al. Limited therapeutic effect of addition of buspirone in fluvoxamine-refractory obsessive-compulsive disorder. *Am J Psychiatry*. 1993;150:647-649.
67. Grady TA, Pigott TA, L'Heureux F, et al. Double-blind study of adjuvant buspirone for fluoxetine-treated patients with obsessive-compulsive disorder. *Am J Psychiatry*. 1993;150:819-821.
68. Pigott TA, L'Heureux F, Rubenstein CS, et al. A double-blind, placebo-controlled study of trazodone in patients with obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1992;12:156-162.
69. Dannon PN, Sasson Y, Hirschmann S, et al. Pindolol augmentation in treatment-resistant obsessive compulsive: double-blind placebo controlled trial. *Eur Neuropsychopharmacol*. 2000;10:165-169.
70. Koran LM, Mueller K, Maloney A. Will pindolol augment the response to a serotonin reuptake inhibitor in obsessive-compulsive disorder? *J Clin Psychopharmacol*. 1996;16:253-254.
71. Blier P, Bergeron R. Sequential administration of augmentation strategies in treatment-resistant obsessive-compulsive disorder: preliminary findings. *Int Clin Psychopharmacol*. 1996;11:37-44.
72. Jenike MA. Drug treatment of obsessive-compulsive disorder. In: Jenike MA, Baer L, Minichiello WE, eds. *Obsessive Compulsive Disorders: Theory and Management*. 2nd ed. Chicago, IL: Year Book Medical; 1990:249-282.
73. Pigott TA, L'Heureux FL, Rubenstein CS. A controlled trial of clonazepam augmentation in OCD patients treated with clomipramine or fluoxetine. New Research Abstract. 144, 145th Annual Meeting of the American Psychiatric Association, Washington, DC, 1992;82.
74. Hollander E, DeCaria CM, Schneier FR, et al. Fenfluramine augmentation of serotonin reuptake blockade antiobsessional treatment. *J Clin Psychiatry*. 1990;51:119-123.
75. Hollander E, Friedberg J, Wasserman S, et al. Venlafaxine in treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry*. 2003;64:546-550.
76. Albert U, Aguglia E, Maina G, Bogetto F. Venlafaxine versus clomipramine in the treatment of obsessive-compulsive disorder: a preliminary single-blind, 12-weeks, controlled study. *J Clin Psychiatry*. 2002;63:1004-1009.
77. Denys D, Van Der Wee N, Van Megen HJ, Westenberg HG. A double-blind comparison of venlafaxine and paroxetine in obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2003;23:568-575.
78. Delrito JA. Valproate pretreatment for the difficult-to-treat patient with OCD [letter]. *J Clin Psychiatry*. 1994;55:500.
79. Joffe RT, Swinson RP. Carbamazepine in obsessive-compulsive disorder. *Biol Psychiatry*. 1987;45:122-124.
80. Cora-Locatelli G, Greenberg BD, Martin J, Murphy DL. Gabapentin augmentation for fluoxetine-treated patients with obsessive-compulsive disorder [letter]. *J Clin Psychiatry*. 1998;59:480-481.

130. Rauch SL, Dougherty DD, Cosgrove GR, et al. Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for obsessive compulsive disorder. *Biol Psychiatry*. 2001;50:659-667.
131. Montoya A, Weiss AP, Price BH, et al. Magnetic resonance imaging-guided stereotactic limbic leucotomy for treatment of intractable psychiatric disease. *Neurosurgery*. 2002;50:1043-1052.
132. Hay P, Sachdev P, Cumming S, et al. Treatment of obsessive-compulsive disorder by psychosurgery. *Acta Psychiatr Scand*. 1993;87: 197-207.
133. Kim MC, Lee TK, Choi CR. Review of long-term results of stereotactic psychosurgery. *Neurol Med Chir (Tokyo)*. 2002;42:365-371.
134. George MS, Post RM, Keeter TA, et al. Neural mechanisms of mood disorders. *Curr Rev Mood Anxiety Disord*. 1997;1:71-83.
135. Van Bockstaele EJ, Peoples J, Valentino RJ. Anatomic basis for differential regulation of the rostrolateral peri-locus coeruleus region by limbic afferents. *Biol Psychiatry*. 1999;46:1352-1363.
136. Malhi GS, Sachdev P. Novel physical treatments for the management of neuropsychiatric disorders. *J Psychosom Res*. 2002;53:709-719.
137. Harden CL, Pulver MC, Ravdin CL, et al. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. *Epilepsy Behav*. 2002;1:93-99.
138. Jobe PC, Dailey JW, Wernicke JF. A noradrenergic and serotonergic hypothesis of the linkage between epilepsy and affective disorders. *Crit Rev Neurobiol*. 1999;13:317-356.
139. Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol Psychiatry*. 2000;47:276-286.
140. Ward H, Ninan PT, Pollack M, et al. Treatment-refractory obsessive-compulsive disorder: potential benefit of VNS therapy. Poster presented at: Annual Meeting of the Anxiety Disorders Association of America. March 27-30, 2003; Toronto, Canada.
141. George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in psychiatry. *Arch Gen Psychiatry*. 1999;56:300-311.
142. Greenberg BD, Rezai AR. Mechanisms and the current state of deep brain stimulation in neuropsychiatry. *CNS Spectr*. 2003;8:522-526.
143. Nuttin BJ, Gabriels LA, Cosyns PR, et al. Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery*. 2003;52:1263-1274.
144. Barker AT, Jalinous R, Freeston IL. Non-invasive stimulation of the human motor cortex. *Lancet*. 1985;1:1106-1107.
145. Greenberg BD, George MS, Dearing J, et al. Effect of prefrontal repetitive transcranial magnetic stimulation (rTMS) in obsessive-compulsive disorder: a preliminary study. *Am J Psychiatry*. 1997;154:867-869.
146. Alonso P, Pujol J, Cardoner N, et al. Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: A double-blind, placebo-controlled study. *Am J Psychiatry*. 2001;158:1143-1145.
147. Martin JLR, Barbanoj MJ, Clos S. Transcranial magnetic stimulation (TMS) for the treatment of obsessive-compulsive disorder (OCD). *Cochrane Database Syst Rev* 2003;3:CD003387.
148. Wasserman EM. Risk and safety of repetitive transcranial magnetic stimulation (report and suggested guidelines from the International Workshop in the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996). *Electroencephalogr Clin Neurophysiol*. 1998;108:1-16.
149. Wasserman EM, Cohen LG, Flitman SS, et al. Seizures in healthy people with repeated "safe" trains of transcranial magnetic stimuli. *Lancet*. 1996;347:825-826.
150. Rudorfer MV. Electroconvulsive therapy in treatment-refractory obsessive-compulsive disorder. In: Goodman WK, Rudorfer MV, Maser JD, eds. *Obsessive-Compulsive Disorder: Contemporary Issues in Management*. London, UK: Lawrence Erlbaum Associates; 2000:431-455.