Experimental Therapeutics for Refractory Obsessive-Compulsive Disorder: Translational Approaches and New Somatic Developments

Heather A. Berlin, PhD, MPH,1 Holly Hamilton, BA1 and Eric Hollander, MD1,2

1Department of Psychiatry, Mount Sinai School of Medicine, New York, NY
2Seaver and NY Autism Center of Excellence, Mount Sinai School of Medicine, New York, NY

ABSTRACT

Significant advances over the past 20 years in our understanding of the phenomenology and pathophysiology of obsessive-compulsive disorder, made in part from structural and functional neuroimaging and genetics research, can guide treatments that target brain regions, circuits, and neurotransmitter systems specific to obsessive-compulsive disorder, the disruption of which may alleviate obsessive-compulsive disorder symptoms. We discuss here our current understanding of the underlying neurobiology and heritability of obsessive-compulsive disorder and integrate that understanding with a review of the current pharmacological, neurosurgical, and brain stimulation treatments of refractory obsessive-compulsive disorder. Expanding on these studies, we hope that new pharmacological and psychological treatment strategies and research-driven targets for lesioning, stimulation, or other types of focal neuromodulation can be identified that could lead to future research directions. Cross-species translational research and neuroimaging of the physiological and anatomical pathways implicated in the pathophysiology and treatment response in obsessive-compulsive disorder will advance our understanding of the neural basis of obsessive-compulsive disorder and lead to more targeted and effective treatment options. Mt Sinai J Med 75:174–203, 2008. © 2008 Mount Sinai School of Medicine

Key Words: caudate nucleus, cingulate gyrus, deep brain stimulation, internal capsule, neurosurgery, obsessive-compulsive disorder, prefrontal cortex, serotonin reuptake inhibitors, therapeutics, transcranial magnetic stimulation.

Obsessive-compulsive disorder (OCD) is a relatively common, chronic illness associated with considerable morbidity and economic and social burden.1–5 OCD is characterized by intense anxiety caused by unwanted, intrusive, persistent thoughts, images or impulses (obsessions), which lead to repetitive behaviors or mental acts (compulsions) that the person feels driven to perform to prevent or reduce his or her distress or anxiety.6 Obsessions and compulsions are time-consuming and cause significant functional impairment and/or distress.7 OCD has a mean lifetime prevalence of approximately 2% to 3% in the general population,8–11 more than twice that of schizophrenia,6 and is the fourth most common mental disorder after depression, alcohol and substance misuse, and social phobia.12 Lifetime and annual prevalence rates of OCD are remarkably similar across cultures.5,9

OCD onset may begin in childhood, adolescence, or early adulthood.13 The mean age of onset is in late adolescence for men and in the early twenties for women, for whom the incidence is slightly higher.6,9 Onset is gradual for most, but acute onset has been noted in some cases. OCD may follow an acute, episodic, or chronic course.14 Most people have a chronic waxing and waning course, with exacerbation of symptoms that may be stress-related. OCD is highly comorbid with a variety of disorders,5 especially anxiety disorders,14–18 depression,19–21 alcohol or substance misuse,22–24 eating disorders,25 and body dysmorphic disorder.26
The most common treatments for OCD are pharmacological and cognitive behavioral interventions. According to the American Psychiatric Association treatment practice guidelines for OCD,27 selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatments for OCD. However, SSRIs are often associated with delayed onset of therapeutic effect (8–12 weeks), only partial symptom reduction, and response failure or intolerability in 40% to 60% of patients. Pharmacological options for SSRI refractory cases include increasing drug dose, changing to another SSRI or clomipramine, combining SSRIs, or changing the mode of drug delivery. Augmentation with second-generation antipsychotics has demonstrated efficacy as a second-line treatment.

Despite this, some patients still remain refractory to all standard pharmacological and psychological treatments. This review primarily focuses on several alternative medical interventions that have been considered for these severe cases, such as ablative neurosurgery, and brain stimulation techniques, such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and the nonablative neurosurgical procedure deep brain stimulation (DBS). The study of translational approaches, including underlying endophenotypes (mediating factors based on the study of neurochemistry, neurobiology, and cognition) and predictive animal models used to investigate genetic factors and drugs with anticompulsivity effects, is crucial to the development of appropriate psychological and somatic treatment methods for refractory OCD and to our understanding of the pathogenesis of the disorder.

To review the relevant original research studies, we conducted a computerized literature search of recent articles (PubMed, 2000 to February 2008, any language) and also included older articles (before 2000) that we deemed relevant. Various combinations of keywords were used. We also considered sources cited in the reports identified by our original search and some key reviews. Given the limited number of available studies in certain areas, particularly DBS, we applied no methodological exclusion criteria. However, given the breadth of these topics and in order to keep the article concise and focused, we report only those publications that we consider most pertinent to and as a framework for the alternative somatic treatments and those publications that were considered by the authors to meet rigorous research standards.

After briefly describing the proposed etiology of OCD in terms of the underlying neurobiology, genetics, and environmental and psychological factors, we go on to discuss animal models that seem most relevant to the development of new treatment approaches for OCD. We then describe standard first-line treatments for OCD and the treatments used for patients who are incomplete responders or nonresponders to serotonin reuptake inhibitors (SRIs). Finally, we discuss treatments for patients who are still treatment-resistant, namely, ECT, TMS, ablative neurosurgical procedures, and DBS, and conclude with a discussion of possible directions for future research.

ETIOLOGY

Neurobiology

Although the cause of OCD is unknown, there is increasing evidence for the involvement of biological factors.4,5 For any individual, a range of factors are likely to contribute to the expression of the disorder. OCD is heterogeneous in terms of the types of obsessions and compulsions, heritability, and comorbid conditions, and this probably reflects heterogeneity in the underlying pathology.28 In accordance, there are many disorders known as obsessive-compulsive spectrum disorders that share features with OCD, such as trichotillomania, Tourette’s syndrome (TS), and body dysmorphic disorder.26

Although the neurobiological basis of OCD (symptoms and related cognitive impairments) is unclear, lesion, functional neuroimaging, and neuropsychological studies have implied that structural and functional dysfunction of limbic or affective corticostriatothalamocortical circuitry, which includes the orbitofrontal cortex (OFC), plays a key role.26–31 These circuits, first identified in nonhuman primates,32,33 have been also been identified in human lesion and imaging studies of OCD patients.34–36 Reduced gray matter volume of OFC in OCD patients compared to healthy controls has been the most consistent finding from structural magnetic resonance imaging (MRI) studies. The OFC is involved in behavioral adaptation to change and motivational aspects of decision making,37 both of which have implications for OCD. Similarities in neurocognitive deficits of OFC lesion38 and OCD patients in a range of cognitive and behavioral tasks involving executive control further implicate the OFC in the pathophysiology of OCD.39 Although studies suggest that OCD patients have increased activity in frontostriatal circuitry, both hypoactivity and hyperactivity of the prefrontal cortex (PFC) may produce deficits in perceptual and cognitive flexibility, but for different reasons.40 There is also imaging evidence, although less consistent, of volume changes in caudate nucleus, anterior cingulate cortex, and medial

DOI:10.1002/MSJ
temporal lobe structures. The inconsistencies in the structural imaging literature may be related to methodological issues (eg, medication effects and small sample sizes), the heterogeneity of OCD, or the comorbidity of the patient samples.

Like structural neuroimaging, functional imaging studies [positron emission tomography (PET), functional MRI, and single-photon emission computed tomography] have implicated several brain areas, including the OFC, the head of the caudate nucleus, and the thalamus. Many studies have shown elevated blood flow/activation in frontal subcortical circuits in OCD patients compared to healthy controls. In particular, PET and functional MRI have shown increased glucose metabolism in the OFC, caudate nuclei, and anterior cingulate in OCD patients. Cortical and basal ganglia regions have been most strongly implicated, but a recent meta-analysis found differences only in the orbital gyrus and the head of the caudate nucleus. Functional imaging data thus far suggest hypermetabolism of frontal regions, and consensus is growing regarding the metabolic states of the caudate and thalamic regions. In general, these findings suggest that frontal and subcortical regions play key roles in OCD, but it is unclear whether these hypermetabolic states are the cause or result of OCD. For a comprehensive review of structural and functional neuroimaging studies of OCD, see Friedlander and Desrocher. The findings are presented in the context of 2 models: executive dysfunction, implicating the dorsolateral PFC, caudate nucleus, striatum, and thalamus; and modulatory control, implicating the OFC, medial PFC, and cingulate gyrus.

However, there are some inherent biases in imaging studies investigating regions of interest (ROIs). They are likely to generate hypotheses related to the regions that they are studying (eg, OFC-striatal circuitry in OCD) but may miss important contributions from brain regions not investigated to date. However, recently developed whole brain–based structural imaging techniques, such as voxel-based morphometry (VBM) and multivoxel analyses, can examine differences in gray matter throughout the brain without the need to prespecify ROIs. These unbiased whole brain (and potentially whole genome) techniques may yield previously unexpected new findings by revealing gray matter differences in areas not considered previously and can be used to confirm the OFC-striatal hypothesis developed in ROI structural MRI studies. Three VBM studies on OCD have been published to date, and consistent with findings from ROI studies, they provide some evidence for orbitofrontostriatal structural abnormalities. However, of the 3 VBM studies report structural changes in parietal regions: the right supramarginal and angular gyrus and the left inferior parietal lobe. Thus, parietal lobe structural abnormalities should perhaps be a target for further investigation in OCD.

Several neurotransmitter systems have been implicated in the pathogenesis of OCD. Many studies demonstrating the efficacy of SSRIs in the treatment of compulsive behavior have supported the role of serotonin in OCD. It has been suggested that OCD patients have excessive baseline activity of excitatory glutamatergic neurons of the OFC, and because serotonin inhibits these neurons, an increased release of serotonin in the OFC may therefore be associated with a decline in OCD symptoms.

Studies investigating serotonin receptor function have also supported its pivotal role, and it has been found that OCD symptoms are exacerbated after the administration of meta-chlorophenylpiperazine, a serotonin 5-hydroxytryptamine receptor 2C (5-HT2C) and 5-hydroxytryptamine receptor 1D (5-HT1D) agonist, and sumatriptan, a 5-HT1D agonist. Recently, Adams et al. found increased 5-hydroxytryptamine receptor 2A receptor binding in the caudate nuclei of untreated OCD patients. The dopamine system also appears to play a role in the pathology of OCD, and many studies have suggested that antipsychotic augmentation in SSRI nonresponders may be an appropriate treatment for refractory OCD. In addition, a recent neuroimaging study found increased dopamine transporter density in the left caudate and left putamen in OCD patients versus controls. Evidence from animal models also points to the role of dopamine in compulsive behaviors (eg, quinpirole-treated rats; see the Animal Models section).

Finally, several lines of evidence suggest that dysfunction in glutamate neurotransmission may contribute to the pathophysiology of OCD, although the precise abnormality in transmission is unknown. An antagonist of the N-methyl-D-aspartic acid glutamate receptor has been shown to worsen the repetitive behavior of transgenic D1CT-7 mice. DICT-7 mice are engineered transgenic mice that express a neuropotentiating protein (cholera toxin A1 subunit) in a cortical-limbic subset of dopamine D1-receptor expressing (D1+) neurons. Furthermore, preliminary studies have suggested that glutamate modulating drugs such as topiramate and riluzole may constitute an effective alternative pharmacological...
strategy for treating OCD; however, further controlled trials are warranted.

**Genetics**

Twin and family studies have provided evidence that genetic factors are involved in the transmission and expression of OCD. Family studies have shown that the risk of developing OCD is 3 to 12 times greater in first-degree relatives than in the general population. Furthermore, concordance for OCD is greater in monozygotic twins (80%–87%) than in dizygotic twins (47%–50%). In a meta-analysis of family and twin studies, a person with OCD was reported to be 4 times more likely to have another family member with OCD than a person without OCD. Genetic and family studies have also shown that OCD appears to be related to tic disorders and TS.

Although twin and family studies implicate a genetic component for OCD, the specific mechanism of inheritance and the genes involved are not known. This may be due to the etiological heterogeneity of OCD. Studies in the 1980s suggested an autosomal dominant pattern of inheritance for the combined phenotypes of OCD, TS, and chronic tics. More recently, have studies have implicated a major locus with a multifactorial genetic contribution. There is some evidence for linkage on chromosome 9p24, but association studies examining candidate genes in the 9p24 region have been mixed. The most promising candidate gene in the region, shared by the 9p24 linkage findings and the reported 9p monosomy, is solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag) member 1 (SLC1A1), which codes for the glutamate transporter excitatory amino acid carrier 1 (excitatory amino acid transporter 3).

Many other studies have shown mixed results in examining genetic loci mainly associated with serotonergic, dopaminergic, or glutamatergic pathways or immunological processes as functional candidate genes for OCD. Genetic polymorphisms of serotonin transporters have been implicated in OCD. This coincides with the effectiveness of SSRIs in treating OCD and with the presence of high concentrations of serotonin receptors within the ventrolateral caudate nucleus. Genetic polymorphisms in the number of variable tandem repeats of dopamine receptor genes, especially the dopamine receptor D4 gene, have also been associated with OCD. This coincides with the efficacy of dopamine blockers for OCD treatment and of dopamine blockers added to SSRIs for some refractory OCD patients and with the functional role of dopamine in basal ganglia structures such as the caudate thought to be involved in OCD. These studies provide further evidence for the involvement of corticostriatothalamic circuits in OCD by suggesting that OCD may be mediated by an inherited dysfunction in serotonin and dopamine systems. Recent genetic association studies of OCD in humans have also implicated genes involved in glutamatergic neurotransmission. This, in conjunction with the synapse-associated protein 90/postsynaptic density-95-associated protein 3 (SAPAP3) study in mice, suggests that defects in excitatory synaptic transmission in the corticostrial circuit may contribute to the pathogenesis of OCD. For a review of human genetic studies of OCD, see Hemmings and Stein.

**Environmental and Psychological Factors**

There are currently no established environmental risk factors for OCD. Several studies have reported major life events in the period preceding the onset of OCD. Some work has demonstrated that psychological trauma may play a role in some cases of OCD. Additionally, pregnancy and the puerperium period have been identified as potential risk factors for OCD, and cases of postpartum-onset OCD have been reported. A recent study found that out of 56 female OCD patients who had been pregnant in the past, 38.2% reported that their symptoms began or changed during pregnancy or within a month of giving birth. Furthermore, Williams and Koran reported that in 7 of 24 women with preexisting OCD, symptoms were exacerbated in the postpartum period. However, rather than the events themselves being causal, a stressful life event may be a trigger in people who are biologically or psychologically predisposed to OCD. The role of stressful life events (including pregnancy and childbirth) as potential risk factors for OCD still needs further investigation.

Some have suggested that streptococcal infection is associated with a form of early-onset OCD. Streptococcal infections trigger an immune response, which in some people generates antibodies that cross-react in the basal ganglia, a region implicated in OCD. However, the link between infections and exacerbation of symptoms is still questionable. For example, 1 study found no relationship between new streptococcal infections and symptom exacerbation in an unselected group of patients with OCD and/or TS.

In terms of psychological models of OCD, some evidence suggests that the way in which people
interpret their thoughts and some of their beliefs, including responsibility, the need to control thoughts, and thought-action fusion, may play a maintaining role in the disorder. However, there is little evidence to date to suggest that these beliefs play a causal role in the etiology of OCD.

Animal Models
Animal models of OCD can be divided into 3 main classes: behavioral, genetic, and pharmacological. We have chosen to discuss here those models that seem most relevant to the development of new treatment approaches for OCD. For a comprehensive review see Joel (2006).

Behavioral Models
Behavioral models were the earliest animal models of OCD and include any naturally occurring stereotypic or repetitive behaviors (ie, tail chasing, fur chewing, and weav ing); innate motor behaviors occurring during conflict, stress, or frustration (ie, grooming, cleaning, or pecking); and learned behaviors that become compulsive (ie, after behavioral manipulation such as signal attenuation–induced compulsive lever pressing).

In terms of naturally occurring stereotypic or repetitive behaviors, Powell et al. showed that deer mice engage in stereotypic behaviors such as patterned running, backward somersaulting, and vertical jumping. In a study by Presti and Lewis, high-stereotypy mice (in comparison with low-stereotypy mice) exhibited significantly decreased enkephalin content and significantly increased dynorphin/enkephalin ratios. The results are consistent with the hypothesis that spontaneous stereotypic behavior is a result of relative hyperactivity along cortico–basal ganglia–cortical feedback circuits involving the direct (facilitative) pathway, but they also suggest that this imbalanced activity involves disruptions of the indirect (inhibitory) pathway. This type of imbalance has been implicated in the compulsions of OCD.

Examples of innate motor behaviors occurring after behavioral manipulation include schedule-induced polydipsia, food restriction–induced hyperactivity, and marble burying. In 1 study, polydipsia was induced in food-deprived rats by exposure to a fixed-time feeding schedule. Interestingly, chronic administration of SSRIs commonly used to treat OCD (ie, fluoxetine, clomipramine, and fluvoxamine) improved schedule-induced polydipsia in rats, whereas other drugs that do not improve compulsive behaviors (ie, haloperidol and diazepam) did not. Altemus et al. treated rats with fluoxetine, imipramine (with no known effect on OCD symptoms), or saline prior to food restriction and exposure to a running wheel. Rats fed for 90 minutes per day could stabilize their weight after an initial decrease; however, if they were given a running wheel, they ran excessively, ate less, and lost weight. Rats receiving fluoxetine lost less weight, ran more, and increased food intake more rapidly than those who received saline. There were no differences in rats receiving imipramine and controls.

More common than schedule-induced polydipsia and food restriction–induced hyperactivity, is marble burying in mice. Rodents commonly use bedding material to bury objects that are both harmful and innocuous, and the discovery that marble burying is reduced by SRIs suggested that the behavior may be related to OCD and compulsive behaviors. Londei et al. suggested that this activity may begin as investigative, and because the marbles are nonreactive, they are unable to provide the necessary stop signal, and this “frustrated” investigation leads to compulsive burying. Similarly, compulsive behaviors may result from an inability to achieve a feeling of task completion. It has been found, however, that burying is also reduced by drugs that do not affect compulsivity, such as diazepam, and this had led to a lack of predictive validity that would accompany a selective response to SSRIs.

The signal attenuation model exemplifies learned behaviors that become compulsive-like after behavioral manipulation and stems from the suggestion that compulsive behaviors result from a failure to stop responding after the successful completion of an action due to inadequate response feedback mechanisms. This may be induced with a post-training signal attenuation paradigm that leads to a pattern of compulsive-like lever pressing. Acute administration of SSRIs (ie, paroxetine and fluvoxamine) but not of drugs that do not improve OCD (ie, desipramine, diazepam, and haloperidol) has been found to decrease compulsive behaviors within the model. Additionally, there is evidence of involvement of the serotonergic and dopaminergic systems in compulsive lever pressing, and strain differences in levels of compulsive lever pressing and resistance to the anticompulsive effect of paroxetine have been thought to parallel strain differences in dopamine and serotonergic function. This, along with evidence of OFC involvement, falls in line with the neural systems implicated in OCD.

DOI:10.1002/MSJ
Genetic Models

Currently, 5 common animal models of OCD (described next) involving observed behaviors of genetically modified mice reflect compulsive and repetitive behaviors that are comparable to symptoms of OCD in humans [see Supplementary Table 3]. Unfortunately, these models are not supported by pharmacological treatment reports, which could prove invaluable in elucidating the neural systems involved in OCD.152

Campbell et al.168 generated transgenic mice that expressed a neuropotentiating enzyme (an intracellular form of cholera toxin) within a cortical-limbic subset of dopamine D1 receptor–expressing (D1+) neurons. These mice, named DICT-7 mice, exhibited compulsive behavioral abnormalities such as perseverance or repetition of normal behaviors, repetitive leaping, and nonaggressive repeated biting of siblings during grooming. The authors emphasized the similarities between the brain regions in which transgene expression was evident in the DICT-7 mice and the neural substrates of human compulsive behavior (ie, the amygdala and limbic areas of the cortex). Another study found that DICT-7 mice exhibit behaviors similar to TS, including juvenile-onset tics and tic responsiveness to clonidine, a drug used in humans for comorbid OCD and TS.169 These results suggest that chronic potentiation of cortical and limbic D1+ neurons may cause compulsive behaviors similar to those in human compulsive disorders,168 providing a transgenic mouse model of OCD and comorbid TS.

Mice with disruption of the homeobox B8 (Hoxb8) gene have been shown to exhibit excessive grooming behavior leading to hair removal and skin lesions, including frequent grooming initiation, increased duration of grooming, and grooming of normal cagemates.170 This aberrant behavior in mutant mice is similar to the grooming common in trichotillomania and OCD, and interestingly, the Hoxb8 gene is expressed in the OFC, anterior cingulate, striatum, and limbic system, all of which are implicated in OCD.

On the basis of previous observations that 5-HT2C receptor knockout (KO) mice not only become obese and hyperphagic but also frequently chew inedible objects,171–173 Chou-Green et al.174 examined 5-HT2C KO mice versus wild-type (WT) mice to look for additional compulsive behaviors, and they observed highly organized repetitive behaviors including frequent chewing (but not eating) of nonnutritive clay, “neat” chewing patterns on plastic mesh screens, and reduced habituation of head dipping in comparison with WT mice. The authors suggested that the organized manner of screen chewing represents an example of compulsive behavior similar to human checking, ordering, smoothing, or washing and that the slower habituation of head dipping may resemble compulsive checking in individuals with OCD. Thus, the authors concluded that the 5-HT2C receptor mutant mouse may provide a promising model of compulsive behavior in humans. Indeed, there is some evidence suggesting that 5-HT2C receptors may have an important role in OCD because 5-HT2C agonists and antagonists have been shown to make OCD symptoms worse,76 although more studies of drugs useful in OCD would still be beneficial to further support the relationship between the behavioral abnormalities in these 5-HT2C KO mice and compulsive behaviors in humans.152

Berridge et al.175 examined the grooming behavior of dopamine transporter knockdown (DAT-KD) mice (whose extracellular dopamine levels in the neostriatum rise to 170% of those in WT rodents) in order to examine whether a behavioral sequence in animals similar to OCD in humans shows sequential stereotypy, which is defined as behavioral patterns of rigid sequential patterns of action involving dysfunction in the nigrostriatal dopamine systems. Monitoring grooming duration and the sequential pattern of the syntactic grooming chain (a fixed-action pattern consisting of 25 grooming movements serially linked in 4 phases and following 1 syntactic rule), the authors found that DAT-KD mice spent more time grooming than WT mice and that the serial pattern of the syntactic grooming chain in DAT-KD mice was strengthened and more resistant to interruption. Because of these observations, the authors suggested several similarities between DAT-KD mutant mice and OCD and TS patients. In sum, DAT-KD mice show aberrant behavior that may be related to disorders involving basal ganglia and dopamine dysfunction such as OCD and TS.

Recently, Welch et al.126 showed that mice with genetic deletion of SAPAP3, a postsynaptic scaffolding protein at excitatory synapses that is expressed in the striatum (see Figure 1), exhibit increased anxiety and compulsive grooming behavior resulting in skin lesions and facial hair loss. Through electrophysiological, structural, and biochemical studies of these mutant mice, the authors revealed deficits in corticostriatal synapses, demonstrating the critical role for SAPAP3 at corticostriatal synapses and highlighting the importance of the corticostriatal system in compulsive behaviors like those of OCD. These behaviors were also assuaged by treatment with an SSRI, and this strengthens this model’s relevance to OCD.

DOI:10.1002/MSJ
Pharmacological Models

Pharmacological models of OCD are based on drug-induced behavioral changes similar to symptoms of OCD, such as perseveration and indecision induced by manipulations of the serotonin system and compulsive checking induced by changes in the dopamine system. The quinpirole-induced compulsive checking model of OCD currently has the strongest face and construct validity. In 1 study, when placed in a large open field with 4 small objects in fixed locations, rats treated chronically with the dopamine agonist quinpirole revisited 2 locations excessively often and rapidly in comparison with those given saline. Furthermore, rats treated with quinpirole have been shown to perform ritual-like behaviors at these object locations. The authors suggested that the behavior of quinpirole-treated rats is similar to compulsive checking in OCD patients because the rats met 5 ethological criteria for compulsive checking that could be suspended for a period of time (as compulsions may be in OCD patients) and because clomipramine was found to partially reduce the behavior. Because dopamine abnormalities have been implicated in some obsessive-compulsive spectrum disorders and behaviors, this model is especially salient on account of its manipulation of the dopaminergic system to induce compulsive checking behaviors.

Summary of Animal Models

A variety of animal models have been proposed for compulsive behaviors and OCD, and each has its own strengths and shortcomings. Because many OCD patients do not respond to SRI therapy alone, it is necessary for a model to demonstrate a lack of effect on compulsive behavior by drugs typically found to not have an effect on symptoms of OCD. The signal attenuation model does have this ability to discriminate between effects of effective drugs and those not known to improve OCD symptoms. Many of the other models discussed here, however, await further pharmacological research to enhance their predictive validity. The signal attenuation model also has strong construct validity stemming from the similarities in its mechanism and in the neural systems involved in OCD psychopathology. The genetic models help identify candidate genes and the neural systems underlying OCD and have strong potential in the realm of anticompulsive drug development, but these too will lack predictive validity until further research is conducted, and the question whether the behavior directly results from the manipulated gene or other targets downstream remains. Combining results of various models may be helpful in elucidating the etiology and neurobiology of OCD and in developing novel treatment strategies.

TRADITIONAL TREATMENTS

The most common treatment approaches for OCD are pharmacological and psychological. Psychoanalytic psychotherapy and psychodynamic psychotherapy were the only psychological treatments for OCD for many years, but there is very little controlled evidence supporting their use. Cognitive behavioral therapy (CBT) was the first psychological treatment for which empirical support was obtained. CBT for OCD can be divided into (1) CBT that relies mainly on behavioral techniques, such as exposure and response prevention (ERP), and (2) CBT that relies mainly on cognitive therapy, such as identifying, challenging, and modifying faulty beliefs. However, these 2 forms of CBT as
well as other cognitive and behavioral treatments generally overlap or are combined in clinical practice and treatment trials. A recent review compared psychological treatments with treatment as usual and found that psychological treatments derived from cognitive behavioral models are effective for adults with OCD.185

Most pharmacological treatments are aimed at regulating serotonin transmission. Serotonergic antidepressants such as clomipramine and SSRIs have been shown to effectively improve OCD symptoms.186–188 In fact, clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline, which are approved by the US Food and Drug Administration (FDA) for treatment of OCD, are recommended as first-line pharmacological agents.27 Because SSRIs are more generally tolerable than clomipramine, an SSRI is usually preferred for a first medication trial.27,189 The specificity of effectiveness of SSRIs in the treatment of OCD suggests that serotonin is an important neurotransmitter involved in the etiology and/or maintenance of OCD. However, studies using an acute tryptophan depletion paradigm have suggested that the treatment of OCD may be less dependent on the synaptic availability of serotonin than the treatment of other conditions such as depression. Acute tryptophan depletion produces a temporary reduction in serotonin synthesis and release, which has been found to cause remitted depression patients who have responded to serotonergic agents to relapse.190,191 OCD patients in remittance, both SSRI-treated192,193 and unmedicated,194–196 however, have been found to evade relapse during acute tryptophan depletion. Therefore, the maintenance of treatment effects on obsessive-compulsive symptoms may not rely solely on the short-term availability of serotonin. Still, SSRIs remain the first-line pharmacological treatment for OCD.

Only 7 randomized trials have directly explored whether the combination of an SRI and CBT consisting of ERP is superior to either treatment alone in adults with OCD, but methodological limitations prevent definitive conclusions.197–205 However, it has been suggested that a combination treatment (SRI plus CBT consisting of ERP) is appropriate when there are co-occurring disorders that are SRI-responsive, when there has been a partial response to monotherapy,204 or when one is trying to reduce the chance of relapse when medication is discontinued.57,205 Some research has indicated that psychological treatments such as CBT are as effective as antidepressants in causing regional brain metabolic changes correlated with OCD symptom improvement.206 Both pharmacological and CBT treatments have been associated with a reversal of the functional neuroimaging findings (in terms of the glucose metabolism rate) to the pattern found in healthy controls.207 However, the exact mechanisms of this reversal are not well understood. Findings suggest changes in caudate nucleus function with pharmacological and behavior therapy for OCD. In 1 study, improvement in OCD treated with behavior modification or fluoxetine hydrochloride was accompanied by significant changes in glucose metabolic rates in the caudate nucleus, as measured with PET.206 Local cerebral metabolic rates for glucose in the head of the right caudate nucleus decreased significantly in comparison with pretreatment values in responders and in comparison with nonresponders and normal controls whose right caudate nucleus metabolism did not change from baseline. In another study, behavior therapy (structured ERP behavioral and cognitive treatment) responders had significant bilateral decreases in caudate glucose metabolic rates that were greater than those in poor responders.207 Furthermore, the pretreatment correlations of brain activity between the orbital gyri and both the head of the caudate nucleus and the right thalamus decreased significantly after effective treatment.

### Treatments for Incomplete Responders or Nonresponders to SRIs

Although considered the first-line and most effective and well-established treatment for OCD,189,208,209 SSRIs are associated with several limitations, including a delayed onset of therapeutic effect (8–12 weeks of treatment to baseline) in most patients, only partial symptom reduction [25%–35% reduction in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)] from baseline in some,210,211 and failure to respond or tolerate SRI treatment (after a single or multiple trials) in 40% to 60% of patients.211–217 Y-BOCS218,219 is an established obsessive-compulsive scale that measures the severity and change in severity of OCD symptoms. Specific criteria used to diagnose treatment resistance have been published elsewhere.212,220,221 SRI-unresponsive OCD patients have substantially impaired social and occupational functioning,212,222,223 and treatment-resistant OCD represents an ongoing challenge for researchers and clinicians. Over the last decade, different forms of treatment have been investigated, including pharmacological augmentation (eg, serotonergic and dopaminergic), psychotherapeutic augmentation, and alternative somatic strategies such as DBS (see the DBS section).

Pharmacological options for SRI refractory cases include increasing the drug dose, changing to another SSRI189 or clomipramine, combining SRIs, and...
changing the mode of drug delivery (eg, intravenous versus oral clomipramine; for a review, see Fineberg and Gale221). However, augmentation with second-generation antipsychotics (dopamine antagonists) appears to be a promising strategy for SRI-resistant OCD. Open and placebo-controlled studies of antipsychotic augmentation of SRI monotherapy have shown very good results225–228 in comparison with augmentation with serotonin-enhancing agents such as lithium, clonazepam, and buspirone.229–233

Randomized, placebo-controlled augmentation trials of both first-generation (haloperidol231,232) and second-generation (risperidone,233–235 olanzapine,236,237 and quetiapine238–241) antipsychotics have yielded response rates of 40% to 55% within 4 to 6 weeks.233–240 Some controlled trials did not find significant differences between antipsychotic and placebo augmentation,237,239,240 but methodological limitations may have contributed to the negative findings. In a recent review of antipsychotic augmentation in double-blind, randomized, controlled clinical trials, one-third of treatment-refractory OCD patients showed a meaningful treatment response to antipsychotic augmentation, and patients with comorbid tics were even more likely respond.242 Still, it remains unclear how long patients need to remain on augmented treatment. A retrospective chart review243 found that 15 of 18 patients (83%) who responded to antipsychotic augmentation relapsed within 1 year after the antipsychotic was discontinued, and 13 of the 15 who relapsed did so by the eighth week after discontinuation.

Some anticonvulsants (eg, valproate, oxcarbazepine, carbamazepine, gabapentin, and topiramate) have been reported to help patients either as monotherapy or as augmentation.244–247 For example, in the first double-blind, placebo-controlled trial of topiramate augmentation of SSRI for the treatment of OCD, our group found that, compared to the placebo group (n = 18), the treatment group (n = 18) exhibited a significantly greater decrease in Y-BOCS compulsions over the 12-week study period with topiramate augmentation.91

### Alternative Somatic Treatments

A minority of people with OCD who remain refractory to all standard pharmacological and psychological treatment (but not exclusively) are considered candidates for several alternative medical interventions such as ECT, TMS, ablative neurosurgical procedures, and nonablative neurosurgical procedures, namely DBS. Vagus nerve stimulation, used for conditions such as depression,248 could also be a potential treatment for OCD, but because it has not been investigated for the treatment of OCD to date, it is not discussed here. The criteria used to establish treatment resistance and to determine eligibility for surgical treatments (stereotactic lesion procedures and DBS) in OCD patients have been published elsewhere221,222,223,224 but include previous and often repeated failed trials of pharmacotherapy and psychological therapies.

Data for the treatment of OCD with these alternative somatic therapies are limited, as there is an understandable scarcity of double-blind trials. It is difficult to perform randomized control trials of invasive procedures with credible sham procedures, so most of the available reports are case series and open-label trials. Consequently, most studies reviewed here were based on a small group of a select sample of patients and were conducted at specific sites, often by a small group of people.250 Although there are more data on stereotactic lesion procedures251 than the other somatic therapies in treatment-resistant/intractable OCD, the cost, irreversibility, and lack of a clear relationship between specific anatomic lesions and successful outcomes limit their use.

In the past decade, there has been increasing interest in brain stimulation techniques in treatment-resistant neuropsychiatric conditions such as OCD and major depression. Stimulating focal brain regions (cortical and subcortical) either directly or indirectly with electrical currents may affect higher cognitive processes and mood systems, and this could explain its efficacy.252 The most widely used brain stimulation technique is ECT, which was introduced in psychiatry over 70 years ago. ECT is one of the most effective treatments for severe, treatment-resistant depression, but its efficacy for the treatment of OCD is not as well established, and given the risks of the procedure and of general anesthesia, it is not clear if the risks outweigh the benefits. Newer methods of electrical brain stimulation, such as TMS and DBS, have a potential advantage over ECT in that they are able to stimulate brain regions more focally.

Mounting evidence from the genetics and imaging literature (discussed previously) suggests that several subcortical structures play a key role in OCD. In accordance, functional modification of these structures may reduce OCD symptoms. Therefore, advances in our understanding of the underlying neurobiology of OCD can guide treatments that target brain regions, circuits, and neurotransmitter systems specific to OCD, the interruption of which may alleviate OCD symptoms. Having discussed our current understanding of the neurocircuitry/neuroanatomy of OCD, we now integrate that understanding with a

DOI:10.1002/MSJ
review of the targets used in ablative and brain stimulation treatments of refractory OCD. Based on the studies reviewed here, perhaps new research-driven targets for lesioning, stimulation, or other types of focal neuromodulation can be identified that could lead to future research directions.112

ELECTROCONVULSIVE THERAPY

ECT is a well-established treatment for severe depression,253 but its efficacy in treatment-resistant OCD is still not established as published data are scarce, come mostly from case-report series, and show mixed results. The studies of ECT in treatment-resistant OCD include a retrospective case series,254 1 open trial,255 and several individual cases256–263 devoid of standardized measures, with some reported degree of effectiveness. However, the lack of standard outcome measures, absence of blinded trials, need for repeated anesthesia, and side effects of ECT preclude it from being a viable option for treatment-resistant OCD without comorbid conditions.27,253 Furthermore, given the high rates of comorbidity in these published cases, ECT may reduce OCD symptoms by treating comorbid disorders such as depression,264 TS,265 and schizophrenia,266 rather than affecting the OCD symptoms directly.

Therefore, given the methodological weaknesses (eg, high comorbidity and no blinded trials) and paucity of convincing evidence for sustained improvement in the ECT studies for treatment-resistant OCD thus far, in addition to the potential risks of ECT, a recommendation for the use of ECT in the treatment of pure treatment-resistant OCD cannot be made at this time.267 However, ECT could be used to target comorbid conditions, such as depression, that might be exacerbating OCD symptoms. Alternatively, magnetic seizure therapy, a type of convulsive therapy in which the electrical stimulus used in ECT is replaced by a magnetic stimulus,268,269 might offer a more focal stimulation with more benign side effects and thus calls for further investigation as it has not yet been tested in OCD patients.270

TRANSCRANIAL MAGNETIC STIMULATION

TMS, a noninvasive technique developed in 1985,271 was first used to treat neuropsychiatric conditions in 1987,272 and since then, an increasing number of studies have investigated its efficacy in a range of neuropsychiatric illnesses.273 TMS delivers magnetic pulses to the cortex via a stimulating coil (handheld or held by an external coil holder) applied directly to the head, which, depending on stimulation parameters [frequency (<1 to 20 Hz), rate, and duration], can enhance or decrease the excitability of the specific cortical region targeted and modify regional cerebral blood flow.277,278 In contrast to ECT, magnetic fields pass through the scalp and skull without the obstruction encountered by direct application of electricity, so less electricity is delivered to the brain in TMS;279 this allows it to stimulate cortical regions more focally and with fewer side effects. Repetitive transcranial magnetic stimulation (rTMS), by which stimulation is delivered in trains of pulses (multiple stimuli per second applied to the same brain area for several consecutive seconds), is typically used in clinical practice. In OCD, TMS aims to modify PFC activity in order to influence obsessive-compulsive symptoms.

In sum, findings from the 4 published rTMS treatment trials for OCD to date [see Supplementary Table 4] are inconsistent, perhaps because of methodological differences between studies. In addition, the samples were small, and there was only 1 double-blind trial. Along these lines, a recent systematic review of TMS treatment for OCD concluded that there was not enough evidence from randomized controlled trials to determine its efficacy.280 Thus, more research is needed to make any firm conclusions about the efficacy of TMS in OCD. Future studies should be better matched in terms of design, stimulation sites, treatment duration, and stimulation parameters. Although limited, the results thus far offer some promise, and the technique’s noninvasiveness in comparison with more invasive techniques such as DBS and neurosurgery, its good tolerability (no dropouts and only temporary mild side effects), the lack of the need for anesthesia, and the relative ease of conducting double-blinded trials should encourage future research to better determine its efficacy.

Given the well-established involvement of subcortical circuits in the pathogenesis of OCD, doubts about the efficacy of TMS in OCD treatment have been raised because TMS penetrates only as deep as 2 cm; this makes the cortex its main target. However, deeper and more distant brain regions may still be affected by this cortical stimulation. In fact, studies combining TMS with functional neuroimaging have shown effects of TMS that are distant from the stimulation site.277,281–283 In addition, coils with deeper penetration powers are being investigated for potential clinical use.284 Doubts have also been raised by the absence of well-established localization...
for the stimulation. There are published reports of symptom reduction after stimulation in both the right and left PFC and the supplementary motor area, but a standardized target area for stimulation is still to be determined. Additional clinical trials could help identify the best position for the coil placement. In practical terms, the need for daily treatment may limit the use of TMS in clinical practice, and clinicians should be prepared for the very rare possibility of a seizure, the most severe adverse event occurring with rTMS, which may be more common at high stimulation frequencies. Hence, if better targets are established via new research and the technology of TMS advances to have a more focal effect, lower frequencies may be used, which may in turn reduce the risk of seizure.

Ablative Neurosurgical Procedures

Neurosurgical treatment for OCD is a highly selective treatment performed for relatively few patients with severe, treatment-refractory OCD when pharmacological and psychotherapeutic alternatives have been exhausted.251 The expert consensus guideline recommends neurosurgery for treatment-refractory OCD as an “infrequently needed, but sometimes life saving intervention” when patients have been nonresponsive to 3 or more trials of SRIs (including clomipramine) and to CBT.189 Of these patients who remain severely ill (∼10–40% of OCD patients),285–287 some are eligible for surgical intervention as long as they meet the appropriate inclusion criteria. The availability of reversible and adjustable DBS (discussed later) may lead to a decrease in the use of ablative neurosurgical procedures. However, these procedures still represent a potentially effective alternative for a select group of patients with very severe OCD.

Reviews of ablative neurosurgery for OCD have described promising results. In 1 study, 58% of 478 patients from 24 studies between 1961 and 1980 showed marked improvement, but more than half of the operations reviewed did not use stereotactic guidance.288 In another review of 12 studies from 1961 to 1988, 67% of the 300 patients reviewed were categorized as “symptom free” or as having “minor symptoms,” and 9 of the 12 studies reviewed used stereotactic guidance.289 Finally, Freeman et al250 found an identical result; that is, 67% of 198 patients reviewed from the 5 studies fell into those categories.

Lesioning for the treatment of OCD is performed mostly via thermocoagulation (the use of heat produced by a high-frequency electric current to destroy tissue locally). The main anatomical targets for lesioning include the fiber tracts that connect the cortex to thalamic nuclei (subcaudate tractotomy), the anterior limb of the internal capsule (anterior capsulotomy; also performed via radiosurgery, which is known as gamma knife capsulotomy), and the cingulate gyrus (anterior cingulotomy). There is also a multitarget procedure in which lesions are made to areas that correspond to those made in both a cingulotomy and subcaudate tractotomy (limbic leukotomies; see Figures 2 and 3). See Supplementary Table 5 for a summary of the literature for the 4 main ablative procedures used in OCD.

In general, the quality of available evidence concerning the efficacy and safety of neurosurgical treatments is variable and inconclusive. There are a variety of design issues that prevent strong inferences from being made. For example, given the relative rarity of these interventions, studies are generally small (preventing identification of predictors of treatment response) and are conducted over long periods of time, and none have control conditions. However, it is unlikely that credible sham procedures would be considered ethical for ablative procedures, and patients are unlikely to accept randomization for these last-resort treatments. Evidence is also inconclusive on whether adverse
changes occur in neuropsychological and personality function in OCD patients who have received neurosurgery.

Furthermore, although there are reports of improvement for the 4 neurosurgical procedures described here, there are also reports of both transient and persistent adverse effects that should be taken into account. Even for studies with the strongest supportive clinical evidence, the proportion of patients who respond must be considered in the context of the potential for serious adverse events inherent in all neurosurgical procedures, including persistent ones as reported in some studies. The entry criteria in the more recent prospective series all include previous failure of pharmacological and psychological (eg, ERP) treatment trials, and this indicates that in general, at least in the last 15 years, these have been considered last-resort treatments.

As a result of contrasting results and varying inclusion criteria, there is also a lack of consensus in the literature on the most appropriate target for ablative surgery, and there is no convincing evidence to date comparing different neurosurgical procedures. Several studies have suggested that multiple lesions may be needed for both cingulotomy and capsulotomy, which may increase the chance of response but may also increase the risk of adverse events. Although stereotactic lesion procedures have more empirical data than the other somatic therapies (discussed later) in patients with treatment-resistant or intractable OCD, the cost, irreversibility, and lack of a clear relationship between specific anatomic lesions and successful outcomes limit their use. Still, for a small number of patients with the most severe, chronic, disabling forms of treatment-refractory OCD, most of whom also have significant psychiatric comorbidity, including severe depression, even the relatively modest degrees and rates of response reported in these studies may be clinically relevant. Therefore, these patients should continue to be assessed as candidates for neurosurgery, which may include nonablative procedures such as DBS (described next).

DEEP BRAIN STIMULATION

The potential long-term adverse effects and irreversibility of ablative neurosurgical procedures led to the investigation of less destructive neurophysiological interventions such as the relatively new technique of electrical DBS. DBS is a nonablative neurological procedure in which electrodes are implanted in the brain to stimulate brain regions directly. The stimulating leads are connected by an extension wire to pulse generators usually implanted under the skin of the chest, just under the collarbone (Figure 4). Stereotactic imaging with MRI and CT are used for the precise anatomical localization of the electrodes. The effects of electrical brain stimulation were previously explored during stereotactic surgery for OCD before lesions were made (eg, see Fux et al). However, the therapeutic use differs in that electrodes are actually implanted in the brain, which are then stimulated by an external electrical source.

Fig 3. (A) Coronal T2-weighted image showing the lesion location in the anterior internal capsule for a capsulotomy using thermocoagulation. Reprinted from Neurosurgery clinics of North America, 14, 267–274, Copyright 2003, with permission from Elsevier. (B) Coronal T1-weighted image showing the location of stimulating electrodes for deep brain stimulation (DBS) in the same location. Reprinted with permission from Lipsman et al. Deep brain stimulation for treatment refractory obsessive-compulsive disorder: The search for a valid target. Neurosurgery 2007; 61: 1–11.
Any lesions that occur during the intervention or through repeated stimulation are not deliberate and are considered to be small with respect to those made deliberately during ablative procedures.

DBS has a number of advantages over traditional lesioning procedures. Because thermocoagulation destroys brain tissue in addition to offering a possible clinical benefit, it can produce harmful, irreversible consequences. In contrast, DBS has a much lower rate of side effects than lesioning with thermocoagulation, and most importantly, DBS can produce a positive clinical effect without creating an irreversible lesion. DBS is reversible, in that the stimulation can be modified (adjusted up or down and delivered intermittently or continuously) at any point after the implantation or discontinued if side effects occur, and the device itself can be removed. The ability to modulate or turn stimulation on and off allows researchers to perform sham stimulations to measure placebo effects; this has not been possible for ethical and practical reasons with ablative procedures.

Therefore, DBS is a minimally invasive neurosurgical procedure that comes with the ability to control side effects from overstimulation and to completely remove the electrode without causing damage to the stimulated region. However, DBS still has risks, and even apparently simple aspects of the procedure can have harmful consequences if it is performed improperly.

The precise mechanisms underlying the efficacy of DBS are still not known (for a review, see Lozano et al. or McIntyre et al.), but they are most likely complex and involve more than just 1 mechanism to achieve the clinical effects observed. By using high-frequency pulses (≥100 Hz), DBS is thought to have complex effects that include a blocking effect on the stimulated area, mimicking the effect of tissue lesioning but without actually destroying tissue. A number of mechanisms have been proposed, such as the release of inhibitory neurotransmitters, synaptic inhibition, depolarization blockade, synaptic fatigue/depression, neural jamming, and stimulation-induced modulation of pathologic network activity. Because the effects of DBS are very similar to those of lesioning, the underlying mechanism probably involves an interruption of pathological neural activity, which varies, depending on the local circuitry and its neurotransmission, and may result from exciting or inhibiting axons and neurons.

Even though its mechanisms are not yet fully understood, DBS has had very good benefits in patients with Parkinson disease (PD) and other movement disorders in terms of reducing abnormal movements, and its efficacy and safety are well established for the treatment of these neurological conditions (see Hamani et al.). Because it is reversible and adjustable, DBS is thought to be a safer, more conservative treatment than lesion surgery for these patients, especially those who need bilateral procedures. In fact, DBS was recently approved by the FDA (in 1997 for unilateral implantation and in 2002 for bilateral implantation) for the treatment of intractable motor disorders (tremor and PD).

The relative success of DBS in the treatment of PD, its reversibility in comparison with ablative procedures, its relatively safe side-effect profile, and the suggested relationship between corticostriatothalamic loop dysfunction–mediated psychiatric and movement disorders have prompted researchers to investigate DBS as an alternative treatment for some psychiatric illnesses, including refractory OCD. DBS was developed as a treatment for OCD through collaboration between Belgian and Swedish researchers. The rationale for using DBS in this population is based on the empirical results of lesion studies and neuroimaging findings in OCD patients showing increased activity in neuronal circuits involving the medial PFC, OFC, anterior cingulate gyrus, and caudate nucleus (or, more generally, in the frontal–basal ganglia–thalamic circuit). Because the blocking
effect of high-frequency DBS on the stimulated area mimics the effect of lesioning tissue. DBS applied to specific regions (eg, the anterior limbs of the internal capsule) theoretically interrupts these hyperactive circuits in the same way as traditional neurosurgical procedures, but without causing irreversible damage to brain tissue.

Studies of DBS for OCD

For a summary of DBS studies for the treatment of OCD, see Supplementary Table 6. In the first published report of DBS for treatment-resistant OCD, 3 of 4 patients who were treated with chronic electrical stimulation instead of bilateral capsulotomy improved (little detail was provided). One of the 3 patients, who had severe OCD for over 20 years, reported an almost instantaneous relief of anxiety and obsessive thinking when stimulation was on, which disappeared when it was turned off. Quadripolar electrodes were stereotactically implanted bilaterally in the anterior limbs of the internal capsules (identical to the target in capsulotomy; Figure 3). DBS of the anterior capsule is thought to disrupt corticostriatothalamocortical loop fibers that connect the cortex and thalamus, which is thought to be a pathological circuit in OCD.

Subsequently, a new series of 6 patients with severe treatment-refractory OCD treated with DBS has been reported in several publications. Again, quadripolar electrodes were stereotactically implanted bilaterally in the anterior limbs of the internal capsules, but this time, 4 patients completed a double-blind crossover trial (ie, the stimulator was continuously on for 3 months and off for 3 months or vice versa in random order) and then had continuous stimulation thereafter. Three of the 4 patients responded (>50% improvement on Y-BOCS and much improved Clinical Global Impression Improvement scores) during the stimulator-on condition versus the stimulator-off condition. Responders reported clinically meaningful improvement in the first week of stimulation, and their symptoms worsened during the course of a few days in the stimulation-off condition. There was a dose-response effect with stimulation, and the stimulation-induced effect (with continuous stimulation) was maintained for at least 21 months after surgery; this made a placebo effect unlikely (a study of PD patients found that the estimated magnitude of the placebo effect in DBS was equivalent to 39% of the magnitude of the effect of active DBS). However, given the small sample size, these results should be interpreted cautiously. Side effects included transient disinhibition with high amplitudes, fatigue, memory disturbances, and weight loss and

DOI:10.1002/MSJ
et al.\textsuperscript{318} chose the shell region of the right nucleus accumbens (NA) as the target for DBS in a pilot series of 4 patients with severe treatment-resistant OCD and anxiety disorders. Because the NA sits between the amygdaloid complex, basal ganglia, medio-dorsal thalamic nucleus, and PFC, which are all involved in the pathophysiology of OCD\textsuperscript{65} and anxiety disorders,\textsuperscript{319} the clinical benefits of anterior capsulotomy may be due to blockage of amygdalo–basal ganglia–PFC circuitry at the level of the shell of the NA rather than at the fiber tracts in the internal capsule.\textsuperscript{318} Therefore, Sturm et al.\textsuperscript{3} implanted the electrodes so that the contacts could alternate between internal capsule and NA stimulation and both sites could be compared. For the first patient in this series, electrodes were implanted bilaterally, and activation of various contact combinations was alternated over several weeks. Stimulation of the right NA produced a significant reduction in symptoms, bilateral stimulation of the NA did not improve the effects, and stimulation of the internal capsule was ineffective. Therefore, the electrode was implanted only unilaterally into the right NA in the subsequent 3 patients.

Three of 4 patients had a nearly complete recovery from both anxiety and OCD symptoms without any side effects with follow-up periods of 24 to 30 months. An MRI of the fourth non-responsive patient showed that the electrode was displaced and missed the target area, and this may explain his lack of response. Although these results are promising, the authors did not state how the initial diagnosis and recovery were attained. Therefore, additional studies with more well-defined methodological information and a larger sample size are needed.

A PET study was conducted under stimulation-on versus stimulation-off conditions in 1 patient from this series.\textsuperscript{318} High-frequency stimulation of the NA shell activated the right dorsolateral PFC and cingulate cortex but inhibited ipsilateral dorsolateral rostral putamen activity. As a central relay structure, the NA may help to modulate information flow from the amygdaloid complex to the amygdala, basal ganglia, mesolimbic dopaminergic areas, medio-dorsal thalamus, and PFC via dopaminergic transmission.\textsuperscript{320–322} On the basis of the overall clinical results of this series and the PET study, the authors suggested that OCD and anxiety disorders result from imbalanced information flow from the amygdaloid complex related to a disturbance in the NA, which modulates amygdalo–basal ganglia–PFC circuitry, and this can be rectified by the blocking of the information flow within the shell of the NA with DBS.

In a recent study from researchers at the University of Michigan,\textsuperscript{323} bilateral DBS of the anterior limbs of the internal capsule was examined in 4 refractory OCD patients. This study consisted of a short-term, blinded, randomized, on-off design of four 3-week blocks and a long-term, open stimulation follow-up (up to 1 year). One patient exhibited marked improvements in mood, anxiety, and OCD symptoms (>55% decrease on Y-BOCS) during the blinded study and open, long-term follow-up. Another patient had moderate benefit during open follow-up. However, amplitude voltages used in the responding patients were on the high end, ranging from 5 to 10.5 V; for example, the patient with the greatest improvement had a setting of 7 V. Side effects were mostly transient and prominent only at high amplitudes and included tingling, nausea, and diarrhea. PET scans showed OFC deactivation in the 2 patients who responded. Thus, the authors suggested that the positive clinical response was mediated by a disruption of the cortical-subcortical circuit. It should be noted that one of the responders committed suicide but left a suicide note stating that her suicide was due to depression and unrelated to the study and that her OCD was still improved. Still, because DBS is often a “last-resort” effort for patients to recapture their “lost” lives, the desperation of patients who qualify for DBS trials may create a risk for suicide. It may also complicate the science of testing efficacy by creating fertile ground for placebo responses. However, placebo effects are rarely long lasting, and OCD is fairly resistant to them.\textsuperscript{325}

Greenberg et al.\textsuperscript{324} reported their results from a collaborative study at Brown Medical School and the Cleveland Clinic on the long-term outcomes of 10 treatment-resistant OCD patients receiving DBS bilaterally in the ventral capsule-ventral striatum. There was a significant positive effect of long-term stimulation (36 months postoperatively) in terms of improved Y-BOCS and Global Assessment of Functioning scores, depression, anxiety, self-care, independent living, and work, school, and social functioning. Four of the 8 patients who reached the 36-month follow-up had a ≥55% decrease in their Y-BOCS scores, and Y-BOCS scores declined between 25% and 35% in 2 patients. Surgical adverse effects included 1 seizure, 1 superficial infection, and an asymptomatic hemorrhage. Psychiatric adverse effects included transient hypomanic symptoms and worsened depression and OCD when stimulator battery depletion interrupted DBS. Still, these results suggest that DBS can have positive long-term effects and is thus a promising treatment option for highly treatment-resistant OCD. A PET study of 6 OCD patients from this series found

DOI:10.1002/MSJ
that acute high-frequency DBS of the ventral capsule/ventral striatum, compared to low-frequency DBS and stimulation-off conditions, increased activation (regional cerebral blood flow) of circuitry implicated in OCD, that is, in the OFC, anterior cingulate cortex, striatum, globus pallidus, and thalamus.312

Finally, 4 recent case reports of open-label DBS325–328 support its efficacy in treatment-resistant OCD patients. In general, positive results were maintained in subsequent follow-up visits for up to 15 months with prolonged stimulation, and there were no serious adverse events. An intimate relationship between various neuropsychiatric circuits is suggested by some of these case studies examining DBS in individuals with comorbid disorders. For example, subthalamic nucleus stimulation in 2 PD patients with severe OCD significantly reduced their PD symptoms as well as their OCD symptoms; this was an unintentional benefit.327 This implicates subcortical structures in the maintenance of OCD and a close connection between neuropsychiatric circuits. Another patient with comorbid major depression and OCD had remission of depression at 6 months and of OCD at 12 to 15 months after DBS of the ventral caudate nucleus, and the benefits continued for the 15-month follow-up period.328 Recent exploration of DBS of the subgenual cingulate for treatment-resistant depression has also yielded positive results.329

Summary of DBS

In sum, DBS has potential value for treating refractory OCD, but additional development work is needed. The results of several DBS trials for OCD are difficult to generalize because of variations in the targets for stimulation and in methodology. The studies thus far have been too small to reach any significant conclusions about efficacy. A more definitive test of the efficacy and tolerability of DBS will require larger, blinded, controlled trials with select patients who meet rigorous inclusion criteria and comprehensive and continuous evaluation of outcome. Fortunately, this relatively nondestructive, reversible intervention makes well-designed controlled trials possible. Therefore, given the preliminary promising results in treatment-resistant OCD and the procedure’s reversibility and adjustability in comparison with ablative neurosurgery, DBS deserves further investigation as it may be an effective therapeutic alternative in select patients with severe, treatment-resistant OCD. However, although DBS clearly has shown some promise and was generally well tolerated in most studies, it is still an invasive procedure with the associated risk of adverse events, both those related to the surgical procedure itself such as hemorrhage, seizure, and infection at the surgical incision site330 and psychiatric adverse events such as DBS-induced acute mood elevation or OCD symptom worsening if DBS is interrupted. Therefore, in the clinic, DBS for psychiatric illness should be used conservatively, and a team of interdisciplinary experts in patient selection, implantation, stimulation, and long-term patient monitoring should be used. Counseling after DBS surgery is also recommended to help patients implement their improvements in daily life.316

The selection of the appropriate target is key for effective DBS for OCD.312 The DBS targets for OCD reported in the literature were selected empirically and/or from an understanding of the presumed pathophysiology of OCD. Several targets have been proposed, including the NA, anterior limb of the internal capsule, ventral portions of the striatum, and ventral caudate nucleus. The differential success of these targets suggests that each may have a distinct role in OCD-related cognitive loops and/or may reflect differences in the study samples. However, the close anatomic relationship between some of these targets and the use of propagating electrical impulses makes overlap likely. The need for high-amplitude stimulation in these procedures suggests that the target is not well circumscribed or that current spread beyond the target is important to elicit the effect. Additional work is needed to identify more specific target regions that are tied to the pathophysiology of OCD. Promising results, similar to those of ablative surgical procedures, have been found with stimulation of the anterior limb of the internal capsule and of the NA. However, there is currently no consensus in the literature on a “gold-standard” DBS target or stimulation amplitude (effective stimulation has ranged from 2 to 10.5 V) for the treatment of OCD. This creates problems for the comparison of studies and the interpretation of results.

The focal and adjustable nature of DBS makes it ideal for offering insights into the neurocircuitry involved in OCD.321 For example, some have suggested that high-frequency DBS in the internal capsule blocks hyperactive circuits of OCD and is related to the observed clinical benefits. Neuroimaging studies312 are starting to investigate exactly how DBS affects these circuits. More accurate, empirically grounded anatomic localization may allow the use of less stimulation to achieve the same clinical benefits.331 Surgically targeting new regions thought to be involved in OCD would offer patients more therapeutic options.112 More research could also be aimed at the development of implantable,
rechargeable batteries with longer lives and better
designed electrodes and stimulation devices.\textsuperscript{331} In
sum, DBS is an important advance in patient care
that may significantly improve the quality of life of
a number of patients who have exhausted almost all
other treatment options.

Treatment-resistant and intractable OCD is still
an important challenge for researchers and clini-
cians. Adjunctive antipsychotics and other promising
somatic treatments such as TMS and DBS need more
investigation to establish efficacy. In recent years,
brain stimulation methods have been defining a “third
path” of treatment outside of traditional pharma-
cological and psychotherapy.\textsuperscript{270} Treatment studies
with brain stimulation techniques (TMS, ECT, and
DBS) in severe, treatment-refractory or intractable
OCD patients have shown varying levels of efficacy
depending on the technique. In general, the level
of confidence in these results is restricted by design
limitations. Studies exploring these techniques for
OCD treatment are limited by small sample sizes and
scarcity of double-blind trials, and none of the alter-
native interventions reviewed here are FDA-approved
for the treatment of OCD. However, given the promis-
ing findings thus far, reversibility, noninvasiveness or
minimal invasiveness, and possibility of double-blind
trials, additional research should be conducted with
TMS and DBS, which may refine these techniques
and establish their efficacy. Larger controlled trials
with select patients meeting strict inclusion criteria
are needed to more definitively test the efficacy and
tolerability of DBS as a potential neurosurgical treat-
ment alternative for refractory OCD. In addition to
the potential of DBS to relieve suffering and improve
the lives of people with OCD, given its focality and
adjustability, it can also be used to investigate the
neurocircuitry involved in OCD.

**FUTURE DIRECTIONS OF TREATMENT**

Current treatment approaches can alleviate OCD
symptoms in some patients, but additional research
is needed to enhance existing treatments and develop
safer and more effective therapeutic options. Studies
are needed to explore whether modifications to
treatment regimens can increase the number of
responders and the rapidity, degree, and endurance
of response. For example, studies could investigate
whether faster titration or higher doses of SRIs result
in more rapid or greater symptom relief. Furthermore,
a number of medications other than SRIs have shown
some efficacy for OCD in preliminary studies, either
as monotherapy or as augmentation (see Table 7).

**Table 7.** Novel Pharmacotherapies That May Be Effective
for Refractory Obsessive-Compulsive Disorder.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoine</td>
<td>Monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>Pindolol</td>
<td>Nonselective beta-blocker</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Piperazino-azepine</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>Opioid analgesic</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Central acting analgesic</td>
</tr>
<tr>
<td>Valproate</td>
<td>Carboxylic acid derivative (anticonvulsant)</td>
</tr>
<tr>
<td>Oxcarbazapine</td>
<td>Dibenzazepine (anticonvulsant)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Carboxamide (anticonvulsant)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>GABA analog (anticonvulsant)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Sulfamate-substituted monosaccharide</td>
</tr>
<tr>
<td></td>
<td>antiepileptic (anticonvulsant)</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>5-HT3 antagonist</td>
</tr>
<tr>
<td>D-Amphetamine</td>
<td>Sympathomimetic amine</td>
</tr>
<tr>
<td>Riluzole</td>
<td>Benzothiazole</td>
</tr>
<tr>
<td>Lithium</td>
<td>Antimanic agent</td>
</tr>
<tr>
<td>Inositol</td>
<td>Carbocyclic polyol</td>
</tr>
</tbody>
</table>

大户：GABA, $\gamma$-aminobutyric acid; 5-HT3, 5-
hydroxytryptamine receptor 3.

As previously discussed, certain anticonvulsants have
been found to help some OCD patients either as
monotherapy or as augmentation agents. In addition,
initial studies on the use of mirtazapine,\textsuperscript{332,333}
phenelzine,\textsuperscript{334} pindolol,\textsuperscript{335,336} ondansetron,\textsuperscript{337}
inositol,\textsuperscript{338,339} riluzole,\textsuperscript{84} D-amphetamine,\textsuperscript{340}
and tramadol\textsuperscript{341} have shown some promising results as
well. However, further study of the efficacy of these
medications in larger randomized, controlled trials
or within the context of proposed animal models
would further enhance the understanding of OCD
treatment as well as its underlying neurobiology.
Additional studies of psychosocial therapies and
the various combinations of these therapies with
medication are also needed. Furthermore, studies
are needed with all treatment approaches to OCD
that will help target specific treatments to individual
patients. For example, the most effective treatment
may vary according to the OCD symptom type
(e.g., contamination, hoarding, and mental compul-
sions) or comorbid condition (e.g., tics, schizotypal
personality disorder, and depression).

Improved understanding of the neurobiological
basis of OCD and of treatment response will help in
the development of new treatment strategies. For
example, identification of susceptibility genes for
OCD could provide insight into the pathogenesis
of OCD, establish a way of identifying those
at risk for developing the disorder, and lead to
the development of more targeted and effective
treatments. Advances in pharmacogenetics, such as
gene chip techniques, could help establish new

DOI:10.1002/MSJ
neurochemical targets for treatment and help to predict responses to or side effects of specific medications or classes of medications. A single-microarray assay, DNA microarray, or gene chip could allow for comprehensive genotyping of thousands of variants in genes involved in drug metabolism, excretion, and transport. Furthermore, because of genetic similarity, the response of first-degree relatives to certain medications may predict the patient's response. Perhaps this can be explored in future research as well because no definitive data are currently available. Other markers (eg, neurocognitive tests, blood, electroencephalogram, and functional and structural neuroimaging) may also aid in understanding the underlying neurobiology of OCD and in identifying early effects that may predict individual treatment response. For example, some small PET studies206,207 have shown correlations between glucose metabolic rates in specific brain areas and OCD symptom response to pharmacological or behavioral therapy.

To date, most attention has been focused on nonhuman primate models of OCD.342 Neuroimaging techniques could be used to look at component features of OCD, such as anxiety, compulsions, and maladaptive thoughts, to help formulate a model of OCD specific to the symptoms of the disorder in humans.69 Many neuroimaging studies have investigated only a limited number of brain areas, and this has biased studies toward verification of well-established models.66 Future neuroimaging studies should more thoroughly examine the brain, using, for example, whole-brain–based imaging techniques to determine whether abnormalities associated with OCD are limited to the corticostriatal circuitry. For example, several recent studies have implicated the amygdala40 and parietal cortices49,73 in OCD, prompting a reconceptualization of current theories of the pathophysiology of OCD. Future studies could also examine the circuitry of highly comorbid disorders with OCD (eg, attention-deficit hyperactivity disorder, other anxiety disorders, and depression) for similarities and differences to provide further insight into the etiology of OCD. Imaging studies should also compare OCD to other commonly comorbid disorders in order to establish the specificity of imaging findings in OCD.342

Genetic models are useful in identifying specific genes and neuroanatomical pathways important in OCD (see Finn et al.345). Although candidate gene studies are promising, they are not yet associated with linkage regions, except for the glutamate transporter gene SLC1A1 in 9p24.344 A number of OCD genetic association studies (case-control and family-based) have implicated genes encoding components within the 5-hydroxytryptamine receptor (5-HT) and dopaminergic systems.127 However, additional innovative research is needed to unravel the precise genetic components of OCD. For example, breaking down OCD symptoms into various dimensions that are continuous with the normal population could help to disentangle the complex inheritance of OCD.345 Furthermore, because there are advantages of gene-based approaches versus single-nucleotide polymorphism–based approaches,346 future studies could employ more complete assessments of candidate genes, possibly using haplotype blocks that span larger regions.127

Animal models have proven invaluable in OCD research, confirming, for example, the importance of the 5-HT157,347,348 and dopamine systems169,349 in the neurobiology and treatment of OCD. Mutant rodent models have provided important information about how genes and the environment interact to affect OCD behaviors via multiple neuropharmacological pathways.343 To date, a number of specific genetically engineered animal models of OCD have been developed. However, their predictive validity is limited by the lack of reports of the effects of pharmacological treatments in these models.153 Despite this, there are several promising genes. For example, mice with genetic deletion of SAPAP3 exhibit increased anxiety and compulsive grooming behavior.126 SAPAP3, a postsynaptic scaffolding protein at excitatory synapses, appears to play a critical role at corticostriatal synapses. This, in conjunction with genetic association studies of OCD in humans implicating genes involved in glutamatergic neurotransmission,115,124,125 suggests that defects in excitatory synaptic transmission in the corticostriatal circuit may contribute to the pathogenesis of OCD. Hoxdb8 mutant mice also show increased grooming behavior,170 and the Hoxdb8 gene is expressed in the OFC, anterior cingulate, striatum, and limbic system, all of which are implicated in OCD.

Although transgenic models have great potential, further investigation is needed to determine whether the subsequent OCD-like behaviors are a direct result of the manipulated gene or are caused by other targets downstream of the gene. We need to know if the gene under investigation is in fact positively associated with the underlying pathology of OCD. Expression array technologies could be employed, which may implicate novel candidates and neurobiological pathways.

The results from genetic studies should be incorporated with clinical and epidemiologic factors to elucidate the cause of OCD. For example, because SRIs are not always effective for OCD,350 a lack of

DOI:10.1002/MSJ
effect in an animal model may reflect an unknown neurobiological basis for compulsive behavior in a subgroup of SRI-refractory patients. Furthermore, separating the afflicted (ie, working with animals that show greater behavioral change in a model and/or after drug treatment) could be beneficial. For a more comprehensive understanding of OCD, multiple animal models will be needed to explore the various aspects of OCD and provide convergent validation of research findings. The development of valid animal models for OCD will increase our understanding of the neural basis of OCD and aid in the development and identification of new therapeutic strategies. Ultimately, animal models can provide new molecular targets for the treatment of OCD in human populations, a key goal of transitional research.

Genetically engineered animal models will be increasingly valuable, in conjunction with new technologies such as RNA interference, gene-chip microarrays, and advanced proteomics, in helping to further our understanding of OCD. Noninvasive neuroimaging (eg, small-animal single-photon emission computed tomography) for exploring the neuroanatomic basis of OCD also offers an exciting future direction, especially if combined with pharmacologic models. Neuroimaging and cross-species translational research of the physiological and anatomical pathways implicated in the pathophysiology and treatment response in OCD will advance our understanding of the neural basis of OCD and lead to more targeted and effective treatment options.

DISCLOSURES

Eric Hollander, MD had research grants from Solvay, Janssen, Bristol-Meyers Squibb, and GlaxoSmithKline in the past.

REFERENCES


DOI:10.1002/MSJ


DOI:10.1002/MSJ


DOI:10.1002/MSJ


187. Soomro G, Oakley-Browne M, Doughty C. Serotonin re-uptake inhibitors (SSRIs) versus placebo for

DOI:10.1002/MSJ


DOI:10.1002/MSJ


