

Treatment Strategies for Chronic and Refractory Obsessive-Compulsive Disorder

Steven A. Rasmussen, M.D., and Jane L. Eisen, M.D.

Obsessive-compulsive disorder (OCD), despite our increasing understanding of its causes and its effective treatment, remains a chronic and underdiagnosed disorder. Both treatment with SSRIs and the behavioral treatment strategy of exposure with response prevention have been proved by clinical trials to be effective and safe in treating OCD; however, even these treatments sometimes elicit only moderate patient response, and some OCD patients do not respond to them at all. Preliminary data suggest that OCD has lifelong persistence and that discontinuation of pharmacotherapy often leads to relapse. Nonetheless, further prospective, controlled, maintenance studies of OCD are needed to determine factors in and predictors of recovery, remission, and relapse. Finally, new procedures for treatment-refractory patients are needed; neurosurgical and new pharmacologic approaches have shown promise in treating these patients and should be studied in controlled trials.

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Over the past decade, a rapidly increasing number of epidemiologic, neurobiological, pharmacologic, and psychosocial studies have dramatically advanced our understanding of the possible causes and treatment of obsessive-compulsive disorder (OCD). The development and clinical application of new pharmacologic and behavioral treatment strategies have significantly improved the prognosis of patients suffering from this chronic and often devastating neuropsychiatric illness. However, in spite of these treatment advances, the majority of patients can expect only moderate improvement in their symptoms, and 20% to 30% of patients remain refractory.¹⁻³ This paper reviews data related to the epidemiology, natural history, and treatment of OCD and suggests directions for further research that is needed to increase our understanding of longitudinal treatment strategies for this chronic condition.

EPIDEMIOLOGY

Until 1980, OCD was thought to be a rare disorder with a poor prognosis. This impression was radically transformed by publication of the National Epidemiology

Catchment Area Survey, which found that OCD had a lifetime prevalence of 2.5% and a 1-year prevalence of 1.3%, 50 to 100 times more common than previous estimates.⁴ Although there were numerous methodological problems with the design of the ECA study, there have now been several subsequent epidemiologic studies that have confirmed these initial prevalence findings.⁵⁻¹⁰ As many as 5 million Americans may be suffering from this chronic disorder that often results in serious functional impairment.

Although widespread media attention has resulted in significant numbers of previously undiagnosed OCD patients presenting for treatment, the disorder remains underrecognized and undertreated. Analysis of service-utilization data from the ECA study has shown that only 40% of OCD patients are treated by mental health professionals.¹¹ Many of these patients initially present to primary care physicians where they go undiagnosed. Often, patients are hesitant to reveal what they consider to be "crazy" or "odd" symptoms to physicians or mental health professionals, even though they may be willing to discuss other anxiety or depressive-related symptoms that they may find more socially acceptable.^{12,13} The reluctance of patients to divulge their obsessive-compulsive (OC) symptoms is compounded by the fact that many mental health professionals, who were trained in an era when OCD was thought to be a rare condition, continue to fail to ask routine screening questions on their mental status examinations for OCD. Because of the phenomenological heterogeneity of the disorder and its extensive comorbidity with other Axis I and Axis II conditions, the diagnosis is easily missed. It is particularly important to screen patients who present with symptoms of anxiety or depression for OC symptoms due to the high comorbidity between OCD and these disorders.

From the Department of Psychiatry and Human Behavior, Brown University School of Medicine, Providence, R.I.

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Reprint requests to: Steven A. Rasmussen, M.D., Department of Psychiatry and Human Behavior, Brown University School of Medicine, c/o Butler Hospital, 345 Blackstone Boulevard, Providence, RI 02906.

The following four screening questions have an 85% sensitivity for OC patients: (1) Do you have to wash your hands over and over? (2) Do you have to check things repeatedly? (3) Do you have thoughts that come into your mind that cause distress and that you can't stop thinking about? (4) Do you need to complete actions over and over until they are just right or in a certain way before you can move on to the next thing? If the answer to one of these questions is positive, the patients should then be screened more fully with the symptom checklist and 10-item severity-rating scale of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).^{14,15}

NATURALISTIC STUDIES

It has been widely accepted since the time of Janet¹⁶ that, for most patients, OCD is a chronic lifelong condition with a waxing and waning course.¹⁶ Early naturalistic studies of obsessive compulsive neurosis¹⁷⁻¹⁹ (see Table 1) suggested that the majority of patients (range, 34%–61%) continued to suffer from the same level of symptoms at follow-up and that only 16% (range, 9%–32%) reported that they were very much improved at follow-up. However, these early studies suffered from numerous methodological flaws including retrospective design, failure to use standardized diagnostic criteria and symptom-severity ratings, as well as failure to assess multiple domains of outcome. In addition, effective behavioral or pharmacologic treatments had not been introduced at the time that the studies were completed.

More recent observational studies have suggested that the prognosis has improved since the development of effective treatments, with 33% to 64% of patients reporting being very much improved at follow-up.²⁰⁻²³ While these are encouraging data, it is important to bear in mind that approximately 30% of patients report minimal or no improvement at follow-up, and the majority of patients continue to have moderate impairment in their social and occupational function secondary to their obsessive-compulsive symptomatology. Additional prospective, longitudinal, observational studies of the course of OCD are needed to further refine what constitutes remission, recovery, and relapse, and to guide clinicians about the long-term clinical management of this chronic condition.

ACUTE TREATMENT STRATEGIES FOR OCD

Most experts in the clinical management of OCD would agree that an integrated approach to treatment that combines a serotonin selective reuptake inhibitor (SSRI) with exposure-and-response prevention leads to the best therapeutic outcome.²⁴ However, there are surprisingly few controlled data to support that clinical impression. It is clear that for the overwhelming majority of OC patients SSRIs are the pharmacologic treatment of choice. Numer-

Table 1. Naturalistic Follow-Up Studies of Obsessive-Compulsive Disorder

Study	N	Mean			
		Follow-Up (y)	VMI* (%)	Improved (%)	No Change (%)
Lewis ¹⁹ (1936)	50	7.5	32	34	34
Rudin ¹⁷ (1953)	130	8.3	12	26	61
Ingram ¹⁸ (1961)	46	5.9	9	30	61
Flament et al ²⁰ (1990)	25	4.4	48	28	24
Leonard et al ²¹ (1993)	54	3.4	43	30	27
Orloff et al ²² (1994)	85	2.1	64	24	12
Eisen et al ²³ (1995)	51	2.0	33	25	41

*VMI = very much improved.

ous multicenter, controlled studies documenting the effectiveness of SSRIs against placebo or noradrenergic reuptake inhibitors have been published.²⁵⁻³⁵

The tricyclic antidepressant clomipramine was the first potent serotonergic reuptake inhibitor proven to have efficacy in controlled trials of OCD.²⁹ Its use has been limited by the typical anticholinergic and antiadrenergic side effects seen with this class of medication. Fluoxetine was the first SSRI to gain Food and Drug Administration (FDA) approval for OCD.³² This was followed by the approval of fluvoxamine,³⁰ sertraline,³⁶ and paroxetine. This now leaves clinicians with a considerable number of choices in the acute pharmacologic management of OCD.

There is no convincing evidence that one SSRI is superior in efficacy when compared to the others.³⁶ However, it appears that individual patients may respond better to one SSRI compared to another. While 60% to 70% of patients have at least moderate levels of improvement following 10 weeks of acute treatment with an SSRI, only 10% are much improved and a third have minimal improvement or no change in symptoms.

Similarly, while it is reported that 60% to 80% of OC subjects are much improved following exposure-with-response prevention, it appears that most patients who have been studied are either handwashers or checkers. In addition, it is estimated that 20% to 30% of patients refuse to enter into behavioral treatment.^{24,37} These findings emphasize the need to gain a better understanding of why patients refuse to enter such treatment and whether motivational techniques can be employed to increase entry into and compliance with exposure techniques. There have been very few controlled trials comparing the efficacy of behavioral pharmacologic and combined approaches to treatment.³⁸⁻⁴⁰

MAINTENANCE AND DISCONTINUATION STUDIES IN OCD

While there is general agreement that the SSRIs should be continued for a minimum of 6 months to 1 year, there

Table 2. Relapse Following SSRI Discontinuation*

Study	N	Design	Relapse (%)	Time of Discontinuation
Pato et al ⁴¹ (1988)	18	Placebo	89	5–27 months
Pato et al ⁴³ (1990)	25	CMI to DMI	64	5 weeks
Leonard et al ⁴² (1991)	12	CMI to DMI	89	4–32 months

*Abbreviations: CMI = clomipramine, DMI = desipramine.

have been no controlled, maintenance studies of the efficacy and safety of the SSRIs in the long-term treatment of OCD. Most of the evidence supporting the need to continue pharmacologic treatment is based on a handful of controlled, discontinuation studies with small numbers of subjects^{41–43} (see Table 2). High rates of relapse (65%–90%) have been found after acute discontinuation of serotonin reuptake inhibitors at varying time periods up to 1 year after initiating treatment. Most clinicians' experience has been that there will continue to be a high rate of relapse that is independent of the time of discontinuation, though there are no controlled data beyond 1 year to substantiate this clinical impression. There is also a general clinical consensus that combining exposure-and-response prevention with pharmacologic treatment will reduce the rate of relapse. Several important questions about the long-term treatment of OCD need to be addressed with controlled studies including: (1) What are the frequency of recovery, remission, and relapse during long-term maintenance with SSRI, exposure, or combined treatments? (2) What are the optional duration and intensity of maintenance treatment in OCD? (3) What is the minimal effective dose of SSRI and behavior therapy to maintain recovery? (4) What is the long-term protective effect of behavior therapy in preventing relapse? (5) What are the predictors of recovery, remission, and relapse?

APPROACHES TO THE TREATMENT-REFRACTORY PATIENT

There is an emerging consensus about the definition of what constitutes a treatment-refractory OCD patient. Most clinicians would define a treatment-refractory patient as someone who has failed both adequate trials of an SSRI and exposure-with-response prevention. An adequate trial of an SSRI is defined as 10 to 12 weeks of continuous treatment at the maximally tolerated dose of drug. An adequate trial of behavior therapy is defined as a minimum of 20 to 30 hours of documented exposure-with-response prevention with no improvement. There can be multiple reasons for failure to respond to initial pharmacologic and behavioral treatment trials. The clinician must be alert to making certain that the patient has been compliant, the dose and duration of treatment have been adequate, the diagnosis is accurate, and the family environment has been adequately assessed. Once these factors have been ascer-

tained, additional trials of SSRIs are warranted. Evidence from the multicenter trials has suggested that for unknown reasons, 20% of individuals who fail to respond to an initial SSRI trial will go on to respond to a second trial of an SSRI.

If an additional SSRI trial(s) fails, consideration should be given to pharmacologic augmentation. When selecting an augmenting agent, particular attention should be given to existing comorbid conditions. Patients with coexisting lifetime multiple tic disorders or schizophrenia-spectrum disorders should be augmented with the addition of a low-dose neuroleptic (e.g., 1–2 mg of haloperidol or risperidone).

McDougle et al. have shown that OC patients with lifetime histories of comorbid tic disorders who have failed an initial SSRI trial respond robustly to haloperidol compared to placebo augmentation and that patients without a tic disorder fail to respond.⁴⁴ In addition, it appears that the subgroup with comorbid tics does not respond as well to SSRIs alone.⁴⁵ Since it is estimated that 15% to 20% of patients with OCD have a lifetime history of tics, it is incumbent upon the clinician to get a careful history of tics in OC patients, particularly those who are refractory to an SSRI. Lithium or ECT augmentation should be considered in patients who are severely depressed in conjunction with their OCD. Finally, benzodiazepine or buspirone augmentation should be considered for patients who present with severe comorbid anticipatory anxiety or panic disorder. One should also consider withdrawing the SSRI and instituting a monoamine oxidase inhibitor (MAOI) in those cases. A systematic approach to augmentation should be followed that ensures adequate dose and duration of treatment.

NEUROSURGICAL OPTIONS FOR THE TREATMENT-REFRACTORY PATIENT

A number of positron emission tomography studies have pointed to abnormalities in circuits that connect the orbitomedial and cingulate cortices to ventral striatum and thalamic nuclei in obsessive compulsives versus controls.⁴⁶ Stereotactic neurosurgical procedures that interrupt frontothalamic connections have been used in intractable OCD since the 1950s. They include cingulotomy, anterior capsulotomy, limbic leukotomy, and subcaudate tractotomy. Studies completed in the 1960s and 1970s suggested that between 50% to 67% of patients were symptom free or very much improved following these procedures⁴⁷ (see Table 3). In addition, the acute risks of neurosurgical intervention were minimal and there appeared to be no long-term alterations in neuropsychological function or personality. Many of these studies failed to follow patients prospectively after surgery and did not utilize careful diagnostic screening or outcome measures with proven reliability and validity. In addition, since ef-

Table 3. Neurosurgical Procedures for OCD*

Procedure	Symptom Free or Very Much Improved
Cingulotomy	56%
Capsulotomy	67%
Limbic leucotomy	61%
Subcaudate tractotomy	50%

*Data from reference 47.

fective pharmacologic and behavioral interventions were not in widespread use at the time, patients who were not treatment refractory by today's definition were probably included in the sample. A recent prospective study of cingulotomy has included these methodological refinements and has studied truly refractory cases.⁴⁸ While the results are more modest than the earlier studies (30% very much improved), it indicates the need for additional studies in this area.

One serious problem with the neurosurgical data has been the inability to conduct controlled studies due to the ethics of a sham procedure that requires the risk of opening the skull. The ethical dilemma has now been reduced by the introduction of the gamma knife. The gamma knife is a radiosurgical device that utilizes gamma ray beams that are emitted from 210 cobalt 60 sources and operates on the principle of a magnifying glass. A destructive lesion can be made at the focal point without affecting surrounding tissue, much in the same way that you can pass your hand underneath a magnifying glass without getting burned provided you are not in the focal plane. Originally developed for treating deep-seated tumors and arteriovenous malformations, it has now been adapted for making lesions in the anterior limb of the internal capsule as it sweeps up through the striatum from the dorsomedial and anterior thalamic nuclei to their projection sites in the orbitomedial frontal and cingulate cortices. The cobalt sources can be easily plugged, allowing for a sham intervention and the ability to keep the investigators and patients blind to whether or not an active intervention is being made. Preliminary pilot data from our site have demonstrated efficacy in 40% to 50% of the treatment-refractory patients receiving the active procedure with no significant acute or long-term side effects. (Rasmussen SA, Jenike M, Mindus P, unpublished observations). In summary, preliminary data suggest considerable efficacy and minimal risks in treating treatment-refractory patients with neurosurgical techniques that interrupt impulse flow from orbitomedial and cingulate cortices to striatum and thalamic projection sites. Further double-blind studies to confirm efficacy and safety are needed.

SUMMARY

In conclusion, OCD is a common, chronic, underrecognized disorder with significant morbidity and functional

impairment. Controlled studies have proven the efficacy and safety of the SSRIs and exposure-with-response prevention, though patients may only experience moderate improvement and not all will respond to these interventions. Preliminary data suggest that OCD is a chronic life-long disorder and that discontinuing pharmacotherapy leads to a significant risk of relapse. The addition of behavior therapy appears to substantially reduce the risk of relapse. However, prospective, controlled, maintenance treatment studies are needed. Finally, additional new approaches to the treatment-refractory patient are needed as well as controlled trials of neurosurgical and new pharmacologic approaches that have appeared promising.

Drug names: buspirone (BuSpar), clomipramine (Anafranil), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), paroxetine (Paxil), risperidone (Risperdal), sertraline (Zoloft).

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