Biologic Approaches to Treatment-Refractory Obsessive–Compulsive Disorder

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Despite advances in the pharmacotherapy and behavior therapy of obsessive–compulsive disorder (OCD), a number of patients experience little or no significant improvement. Although the effectiveness of serotonin reuptake inhibitors (SRIs) is well established, between 40% and 60% of patients are nonresponders. Even among "responders" to SRIs, the magnitude of response is usually incomplete, with few patients becoming asymptomatic. In clinical trials, a 25% to 35% decrease in Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) scores from baseline is often used to define the threshold for a categoric response to treatment. Although this degree of change represents a clinically meaningful reduction in symptom severity, there remains considerable room for improvement. This article focuses on medical approaches to the patient with OCD who is either a nonresponder or a partial responder to treatment with SRIs. The current state of knowledge regarding the efficacy of these approaches is summarized and recommendations are made based on empirical evidence and the clinical experience of the authors.

DEFINITIONS OF TREATMENT RESISTANCE

Various terms have been used to describe patients who have failed treatment, but there is no universal agreement on a recommended nomenclature. For the purposes of this review of biologic therapies, the term "treatment resistant" will generally be applied to those patients who have not shown a satisfactory response to adequate trials of at least two SRIs. The terms "treatment refractory" or "intractable" connote greater degrees of treatment resistance as reflected in failure to respond to a variety of anti-OC treatment strategies (including combinations of agents) as well as behavior therapy.

The classification of patients as treatment failures is critically dependent on the definition of response that is used. Most recent studies have used change scores on the 10-item Y-BOCS (range = 0 [no symptoms] to 40 [extreme symptoms]) as the primary outcome measure. The majority of large-scale drug trials have used a 25% or greater decrease from baseline in Y-BOCS score to define a responder. The clomipramine hydrochloride (CMI) multicenter trials set a higher threshold of a 35% reduction in Y-BOCS scores to meet response criteria. Some studies have required responders to achieve a "much improved" or "very much improved" rating on the Clinical Global Impressions scale in addition to meeting Y-BOCS criteria. Nevertheless, a problem with using "change" criteria alone is that a patient who is classified as a responder may still have clinically significant symptoms of OCD at the conclusion of the trial. For example, a patient who started out severe (baseline Y-BOCS = 30) may be counted as a responder using a 35% reduction in Y-BOCS scores but may still have moderate symptoms (Y-BOCS = 19.5). The latter example might be better categorized as a "partial responder," reserving the term "responder" for those who achieve an endpoint below a pre-established severity level (eg, Y-BOCS = 16).
REASONS FOR TREATMENT RESISTANCE

Different factors may account for the failure of a patient with OCD to respond to a potent SRI. First, the adequacy of the acute drug trial must be evaluated. Was the duration of the trial long enough or the dose sufficient? Although there is consensus among experts that the duration of an adequate medication trial must be between 10 and 12 weeks, there is less uniformity of opinion with regard to what constitutes an adequate dose. Some, but not all, fixed-dose trials of selective SRIs indicate that higher doses are significantly superior to lower doses in the treatment of OCD. In the case of paroxetine hydrochloride in OCD, 20 mg daily did not separate from placebo; the lowest effective dose was 40 mg daily. By and large, studies of fluoxetine hydrochloride in OCD suggest that 60 mg daily is more effective than 20 mg daily, but that 20 and 40 mg daily are more effective than placebo.

In the final analysis, the criteria for an adequate trial must be defined in terms of the medication(s) in question. Adequate trials in OCD of CMI, fluvoxamine maleate, fluoxetine hydrochloride, sertraline hydrochloride, and paroxetine hydrochloride require a minimum daily dose of 150, 150, 40, 150, and 40 mg, respectively, for at least 8 weeks of the 10- to 12-week trial. Although a trial of fluoxetine with 40 mg daily for 8 of 12 weeks might be deemed adequate, a nonresponder to such a trial should not be labeled as fluoxetine resistant until the dose is increased to 80 mg daily or tolerated. Another potent and selective SRI, citalopram, was recently introduced for the treatment of depression in the United States. Although one would predict citalopram's efficacy in OCD based on its mechanism of action, formal studies have not been conducted.

Some estimate of compliance is helpful in determining whether the trial was adequate, as indicated by drug plasma levels or pill counts. To date, clinical trials have failed to demonstrate a direct relationship between SRI plasma levels and response in OCD. However, as discussed later in this article, it may be advisable to monitor CMI plasma levels when used in combination with other drugs. Once the adequacy of a trial has been established, other explanations should be sought for cases of treatment resistance. Possible reasons for variability in drug response include effects of comorbid conditions, differences in underlying biology, and psychosocial factors that can impact treatment. There is evidence that certain comorbid conditions are associated with a lower treatment response rate. OCD patients with schizotypal personality disorder appear to have a relatively worse outcome. Studies indicate that the response of OC symptoms to SRIs is generally independent of the presence or severity of coexisting depression. Another study suggests that the response rate to SRI monotherapy is lower in OCD patients with a chronic tic disorder. Patients with a clinical subtype of OCD referred to as primary obsessional slowness—characterized by pervasive slowness in performing routine activities, pathologic doubting, and checking—seem to be less responsive to treatment.

A careful differential diagnostic assessment should precede a drug trial. It is especially important to distinguish between OCD and the Axis II condition obsessive-compulsive personality disorder (OCPD), because there is little evidence that the latter responds to pharmacotherapy. Even apparently classic and uncomplicated cases of OCD demonstrate a variable response to SRI monotherapy. Variability in drug response raises the possibility that OCD is heterogeneous with respect to pathogenesis. Accidents of nature furnish direct evidence for this premise. Numerous clinical reports document that injury to structures of the basal ganglia can produce OC symptoms. Currently, however, one cannot rely on putative clinical subtypes of OCD to predict whether an individual patient will respond to SRI treatment. Even patients with OC symptoms secondary to an acute brain insult may show symptomatic improvement with SRI treatment.

DOSAGE ESCALATION AND SWITCHING ANTIDEPRESSANTS

If a patient has had a limited response but few side effects with an SRI, the next logical step is to increase to the highest recommended dose. Fortunately, the selective SRIs are generally safe even at high doses. In contrast, CMI should not be administered in doses greater than 250 mg daily without careful medical monitoring (eg, serial ECGs) and unless clinically indicated. The risk of seizures associated with CMI increases significantly with doses greater than 250 mg daily. The anti-OC efficacy of supramaximal (recommended above) doses of selective SRIs has not been formally studied, although case reports have shown beneficial results using this approach.

Several different authors of literature reviews on the pharmacotherapy of OCD have advocated changing to a different SRI if there has been no improvement at all following an adequate trial with one SRI; if there have been partial gains, a combination treatment approach is generally recommended instead. Naturally, if the patient does not tolerate one SRI, it is advisable to try a different one, selected on the basis of the expected side effect profile. Sometimes two or more SRIs need to be tried to identify the agent that is most effective for that particular patient.

The starting point for most pharmacologically treated patients is a trial with a selective SRI rather than with the nonselective SRI CMI. Based on recent head-to-head studies, CMI shows no advantage in efficacy over selective SRIs, whereas the selective SRIs are generally better tolerated than CMI. Given equivalent efficacy and the superior safety/tolerability of selective SRIs, it is hard to justify commencing treatment with CMI unless the patient has had
a history of a good response to this drug. These practical considerations notwithstanding, it is the opinion of the authors that some patients respond preferentially to CMI and therefore that no patient should be declared treatment resistant in the absence of a CMI trial.

Based on some intriguing case reports, a trial with a monoamine oxidase inhibitor (MAOI) showed promise in OCD patients with comorbid panic disorder. More recently, Jenike et al. tested the hypothesis that comorbid anxiety may predict response to an MAOI in a 10-week double-blind, placebo-controlled trial of phenelzine sulfate (60 mg daily) versus fluoxetine (80 mg daily). Fluoxetine was significantly superior to both placebo and phenelzine in this trial. Phenelzine was no more effective than placebo, including in the subset of patients with prominent anxiety symptoms. It is the opinion of the authors that MAOIs should be reserved as a distant second-line approach in treatment-refractory OCD.

Several novel medications have been introduced for the treatment of depression, but their value in the treatment of OCD has not been established. Venlafaxine hydrochloride inhibits the reuptake of both serotonin and norepinephrine without significant affinity for muscarinic, histaminergic, or noradrenergic receptors. Case reports and open-label studies support the efficacy of venlafaxine hydrochloride in OCD. In contrast, venlafaxine was not significantly better than placebo in a double-blind trial in 30 patients with OCD. The relatively short 8-week duration of treatment is a limitation of this study. Together, these published reports seem to warrant additional testing of venlafaxine in OCD under double-blind conditions for 10 to 12 weeks of treatment.

Nefazodone hydrochloride is structurally related to trazadone hydrochloride, but has a somewhat different pharmacologic profile and less propensity for inducing sedation. Early pilot studies of nefazodone hydrochloride in OCD were suspended, apparently because of lack of efficacy (Pigott T, Goodman WK, Ramussen SA, unpublished data, 1991). The use of nefazodone was implicated in the emergence of OC symptoms in a patient being treated for depression.

COMBINATION STRATEGIES: ADDING ANOTHER TREATMENT TO THE SRI

The patient who has had a partial response to SRI monotherapy or failed to show any improvement following two consecutive trials with different SRIs is a candidate for combination treatment.

SRI Plus Behavior Therapy

Although it is believed that a combination of an SRI and exposure/response prevention is the most broadly effective treatment for OCD, support from double-blind, placebo-controlled studies is still sparse. In fact, few studies have adequately addressed the question of whether a potent SRI plus behavior therapy is superior to either treatment alone. The studies that have examined this question either suffer from methodologic shortcomings that hamper data interpretation or do not show clear advantages of combined SRI-behavior therapy over SRI therapy alone.

SRI Plus Agents That May Alter Serotonin Function. To date, the rationale for the majority of drug combination strategies has been to add agents to ongoing SRI therapy that may modify serotonergic function, such as tryptophan, fenfluramine hydrochloride, lithium, or buspirone hydrochloride. The addition of clonazepam, pindolol, or another SRI is also discussed in this section.

Adding Tryptophan. Addition of tryptophan, the amino acid precursor of serotonin, has been reported helpful in an OCD patient treated with CMI. Adverse neurologic reactions resembling the serotonin syndrome seen in laboratory animals have been reported when tryptophan is used in combination with fluoxetine. Currently, oral tryptophan supplements are not readily available in the United States because of evidence linking some of these preparations to the eosinophilia myalgia syndrome, a serious and potentially fatal hematologic/nectonotic tissue illness. Blier and Bergeron of McGill in Canada, where tryptophan is widely available, described the benefits of adding tryptophan to a subgroup of patients treated with OCD taking a combination of an SRI and pindolol (discussed later in this article).

Adding Fenfluramine. In open-label studies, both d,l-fenfluramine and dexfenfluramine have been reported beneficial when used as adjuncts in cases of OCD unresponsive to SRIs. Both drugs are serotonin releasers and reuptake blockers that were used in the past as anorectic agents. In September 1997, the manufacturer of d,l-fenfluramine and dexfenfluramine voluntarily removed these products from the market worldwide after reports of serious cardiac complications (carcinoid-like valvular changes).

Adding Lithium. Co-administration of lithium is a proven method for enhancing the thymoleptic action of antidepressants in patients with depression. Lithium has been hypothesized to potentiate antidepressant-induced increases in serotonin neurotransmission by enhancing presynaptic serotonin release in some brain regions. Despite several earlier encouraging reports, the efficacy of lithium addition has not been corroborated in controlled trials. Although the overall yield is low in OCD, individual patients, particularly those with marked depressive symptoms, may benefit from lithium augmentation.

Adding Buspirone. In open-label studies, addition of the serotonin type 1A agonist buspirone to ongoing fluoxetine treatment in patients with OCD led to greater improvement in OC symptoms than did continued treatment.
with fluoxetine alone. These initially encouraging findings have not been corroborated by three subsequent double-blind trials.37-39

Adding Clonazepam. The benzodiazepine clonazepam is not generally considered a serotonergic agent. However, there is evidence from studies in both animals and humans that clonazepam may possess serotonergic properties not shared by other benzodiazepines.40 A number of clinicians maintain that addition of clonazepam to ongoing SRI therapy is helpful in reducing symptoms of OCD, but substantiation by published reports is limited.41 Although existing literature furnishes limited support for the anti-OC efficacy of adjuvant clonazepam, it seems worthwhile to conduct additional studies with longer durations of combined treatment.

Adding Trazodone. In addition to weakly inhibiting serotonin reuptake, the antidepressant trazodone and its major metabolite chlorophenylpiperazine are active at a number of different neuroreceptors, including several serotonin receptor subtypes and alpha adrenergic receptors. In clinical practice, low-dose trazodone is often used as a sedative-hypnotic in conjunction with activating SRIs such as fluoxetine.42 Whether this combination confers any direct anti-OC benefit remains to be established in controlled studies.

Adding Pindolol. Studies in laboratory animals suggest that antidepressant-induced enhancement of serotonin (5-hydroxytryptamine [5-HT]) neurotransmission does not occur immediately because of 5HT1 autoreceptor-mediated inhibition of firing rate and release. Artigas et al.,43 hypothesized that addition of an agent that blocks somatodendritic 5-HT1A autoreceptors might accelerate or augment the action of antidepressants in humans. According to some studies, the β antagonist pindolol acts as a 5-HT1A antagonist at presynaptic sites. In depressed patients, addition of pindolol to antidepressants has been reported to potentiate or hasten response in some,44 but not all studies.45

In OCD, experience with adjunctive pindolol has also been mixed. An open-label study by Koran et al.46 combined pindolol with an SRI in 8 OCD patients who did not show a satisfactory response to the SRI alone. Only 1 of the 8 patients responded. In another open-label trial, Blier and Bergeron47 added pindolol (2.5 mg three times a day) to ongoing SRI treatment of 13 patients with OCD who had not improved with SRIs alone. Four weeks of combined pindolol–SRI treatment had an antidepressant effect in patients with depressive symptomatology, but did not reduce the severity of OC symptoms as reflected in mean scores on the Y-BOCS. Examination of individual Y-BOCS score data did reveal clinical improvement of OC symptoms in 4 of 13 patients, but overall there was no significant group effect of pindolol addition. Addition of tryptophan to the SRI–pindolol combination was associated with significant improvement in OC symptoms after 4 weeks of treatment.29 These encouraging results with triple therapy (SRI–pindolol–tryptophan) need to be verified in double-blind, placebo-controlled trials. Byerly and Goodman reported preliminary findings from an ongoing double-blind, placebo-controlled study of 12 weeks of fluoxetine with or without pindolol.48 The patients in this trial were not classified as treatment resistant; the main objective was to assess whether pindolol hastened response to fluoxetine. Analysis of the first 12 patients showed a trend toward a more rapid response and greater reduction in OC symptoms in the fluoxetine plus pindolol group.

It is noteworthy that pindolol displayed agonist (not antagonist) effects at the 5-HT1 autoreceptor in a recently published study.49 If confirmed, these findings imply that pindolol is not the appropriate agent to be testing the hypothesis of Artigas et al.

Combining SRIs. In clinical practice, a number of SRI-resistant OCD patients receive simultaneous treatment with two selective SRIs. However, there is scant empirical or theoretical support for this strategy. The advantage of dual selective SRI therapy over a higher dose of a single agent is difficult to explain based on our current understanding of their pharmacodynamic properties (ie, common mode of action via inhibition of 5HT transport). Suitable empirical studies would require a high-dose selective SRI monotherapy control group and double-blind conditions.

A more heuristically appealing strategy is the combination of a selective SRI and CMI. There have been encouraging case reports of coadministering CMI with fluoxetine49.50 to minimize unwanted CMI-induced side effects. Combining CMI and fluvoxamine may offer special advantages as well as risks.51 Fluvoxamine, a potent inhibitor of cytochrome P450IA2, inhibits the N-dealkylation of CMI to desmethylclopropamine (DCMI) and thereby reverses the ratio of DCMI:CMI such that the concentration of the parent exceeds that of its metabolite. Under normal circumstances, plasma concentrations of DCMI exceed those of CMI during chronic drug administration. CMI, a more potent blocker of 5HT transport than DCMI, is also thought to be more potent as an anti-OC agent. However, given the absence of adequate efficacy studies and possible risks (ie, seizures and cardiac conduction delays), combined CMI–fluvoxamine treatment should be reserved for severe and highly treatment-refractory cases. If the combination is used, CMI/DCMI levels should be monitored, an anticonvulsant such as clonazepam should be prescribed prophylactically, and serial ECGs should be obtained.

Adding Desipramine Hydrochloride. Some authors have suggested that CMIs dual inhibition of serotonin and norepinephrine transport may contribute to its anti-OC efficacy. If true, then one might predict that a combination of
selective SRI and a selective norepinephrine reuptake inhibitor (such as desipramine hydrochloride) would mimic the effects of CMI. Barr et al.52 investigated the addition of desipramine hydrochloride or placebo in a double-blind fashion for 23 OCD patients who were treated with fluvoxamine, fluoxetine, or sertraline and failed to respond to 10 weeks of monotherapy with the selective SRI. No significant overall differences were found between the two treatment groups in either OC or depressive symptoms.

**SRI–NEUROLEPTIC COMBINATIONS**

**Conventional Neuroleptics**

Monotherapy with these agents is not indicated in OCD, but there is evidence that conjoint SRI–neuroleptic treatment may be beneficial in a subset of patients.53 To date, the putative subgroup that has received the most attention has been OCD with a comorbid chronic tic disorder. This strategy has been based on evidence linking some forms of OCD with Tourette’s syndrome (TS), coupled with the efficacy of standard neuroleptics in suppressing tics.54 Results from a double-blind, placebo-controlled study of haloperidol decanoate addition to fluvoxamine-refractory patients with OCD support the efficacy of this combination treatment strategy.55 Thirty-four patients who had an unsatisfactory response to 8 weeks of fluvoxamine monotherapy were randomized to either 4 weeks of haloperidol (N = 17) or placebo (N = 17) in addition to a fixed daily dosage of fluvoxamine. Mean daily dose of haloperidol at the end of the 4-week trial was 6.2 ± 3.0 mg. The fluvoxamine–haloperidol combination was significantly superior to the fluvoxamine–placebo combination. As predicted, most of the benefit of haloperidol addition to fluvoxamine occurred in the OCD patients with a coexisting chronic tic disorder. It should be emphasized that none of these patients was psychotic. Benefit of neuroleptics in OCD cases with schizotypal personality disorder has not been established.

**Newer Neuroleptics**

Because of the limited effectiveness and tolerability of conventional neuroleptics in TS, clinicians have turned to a new generation of neuroleptics that have been introduced for the treatment of schizophrenia. Risperidone is a member of a class of antipsychotics that block both DA and 5HT receptors. It is being widely used by clinicians to treat tic disorders as encouraging reports appear in the literature.56–58 A number of preliminary reports suggest that risperidone might alleviate OC symptoms when added to ongoing SRI therapy.57,58–62 Specific clinical features predictive of response to a risperidone–SRI combination remain to be established. There is an impression, however, that the response may not be restricted to patients with comorbid tics. Experience with other new generation neuroleptics such as olanzapine is too limited to draw conclusions about indications for use in OCD. The prototypic atypical neuroleptic clozapine was found ineffective when given alone to 12 patients with treatment-resistant OCD.63

**Table**

**Novel Drug Treatments**

Worthy of further study
- IV clomipramine
- Inositol
- Amnuglutethimide (steroid suppressant)
- Immumomodulatory agents
- Antimicrobial treatments
- Gene therapy

Apparantly ineffective
- Oxytocin
- Anticonvulsants (other than clonazepam)
- Antiandrogens
- Thyroid hormone
- Stimulants
- Clonidine
- Clozapine

**Novel and Experimental Drug Treatments**

A variety of alternative drug treatments have been used in OCD (Table). Of those considered here, intravenous CMI is the only treatment supported by a reasonable degree of empirical evidence. Several open-label trials suggest that intravenous administration of CMI may be helpful in patients refractory to oral CMI.64,65 Two double-blind trials66,67 lend support to the efficacy of intravenous CMI in treatment-refractory patients. Disadvantages of this experimental technique are its availability at only a few research settings and limited information on its long-term benefits.

The possible role of hormones and neuroleptics in the treatment of OCD has begun to be explored, but preliminary findings are not encouraging. Four weeks of adjuvant triiodothyronine treatment was ineffective in 16 patients with OCD who had had a partial response to CMI.68 Preclinical studies suggest that the neuroleptic oxytocin mediates a number of behavioral effects that may be related to OC behavior in humans,69 including inhibiting the acquisition of aversive conditioning. Anseau et al.70 reported a case of OCD in which 4 weeks of intranasal administration of oxytocin led to improvement in OC symptoms, but the side effects were profound, including memory disturbances, psychosis, and somatic abnormalities. In another study, oxytocin was ineffective in reducing symptoms of OCD.71 In a small study of females with OCD, the antiandrogen cypro-
terone acetate seemed to exert an anti-OC effect, but it was not sustained. An attempt by another group to replicate this finding in a woman with severe OCD was unsuccessful.

Recent studies on the therapeutic use of the second messenger precursor inositol have been extended to OCD. The design was based on the successful inositol treatment of depression and panic disorder under double-blind, placebo-controlled conditions. Fux et al. entered 15 OCD patients who had failed previous treatment with CMI or selective SR1s into a double-blind, controlled crossover trial of 18 g/day of inositol or placebo for 6 weeks each. There were no reported side effects and 13 patients completed the protocol. Y-BOCS scores were significantly lower when subjects were taking inositol compared with when they were taking placebo. The mechanism of action of inositol is unclear, but warrants continued interest and replication.

Addition of the steroid suppressant aminoglutethimide to fluoxetine led to significant improvement in a case of treatment-refractory OCD. The rationale for this approach was based on evidence that steroids contribute to the maintenance of the depressed mood state and that steroid suppressant agents may be useful in cases of treatment-resistant depression.

It has been proposed that some cases of childhood-onset OCD may be related to an infection-triggered autoimmune process similar to that of Sydenham's chorea, a late manifestation of rheumatic fever. More than 70% of cases of Sydenham's chorea have OC symptoms. The etiology of Sydenham's chorea is thought to involve the development of antibodies to group A β-hemolytic streptococcal (GABHS) infection that cross react with basal ganglia and other brain areas. Swedo has coined the term PANDAS (pediatric autoimmune neuropsychiatric disorders associated with strep) to describe cases of childhood-onset OCD that resemble Sydenham's chorea with respect to acute onset following a GABHS infection, accompanying neurologic signs, and an episodic course. Various trials with immunomodulatory treatments (eg, prednisone, plasmapheresis, IV immunoglobulins) or antimicrobial prophylaxis (eg, penicillin) are under way at the National Institute of Mental Health and elsewhere for putative PANDAS cases. This exciting new avenue of research will undoubtedly be the subject of intense investigation during the next few years.

Nonpharmacologic Biologic Approaches

Nonpharmacologic biologic treatments of OCD have included electroconvulsive therapy (ECT), neurosurgery, sleep deprivation, phototherapy, and repetitive transcranial magnetic stimulation (rTMS). ECT, regarded as the gold standard for treating depression, is generally viewed as having limited benefit in OCD despite sporadic reports of its success in treatment-resistant cases. In some instances, the favorable response to ECT was short-lived. Khanna et al. described 9 treatment-refractory OCD patients (without depression) who underwent ECT, resulting in a decline in global OCD ratings exceeding 20%. However, all had returned to their baseline illness by 4 months. ECT should certainly be considered in the treatment of depressive symptoms in the treatment-refractory OCD patient at risk of suicide.

Modern stereotactic surgical procedures should not be equated with the relatively crude neurosurgical approaches of the past. Recent evidence suggests that stereotactic lesions of the cingulum bundle (cingulotomy) or anterior limb of the internal capsule (capsulotomy) may produce substantial clinical benefit in some patients with OCD without causing appreciable morbidity. In a prospective follow-up study of 33 OCD patients who underwent cingulotomy, Jenike et al. found that 25% to 30% of the patients experienced substantial benefit according to conservative criteria. In a more recent prospective study, Baer et al. evaluated 18 OCD patients before and after bilateral cingulotomy. Five patients (28%) met conservative criteria for treatment response. A number of unanswered questions about neurosurgical treatment of OCD remain: (1) What is the true (placebo-corrected) efficacy of surgery?; (2) Which procedure (ie, cingulotomy, capsulotomy, limbic leucotomy) is best?; (3) What is the optimal placement of lesions?; and (4) Can we predict who are the best candidates for surgery?

Currently, stereotactic neurosurgery should be viewed as the option of last resort in the gravely ill patient with OCD who has not responded to well-documented adequate trials during a 5-year period with several SRIs (including CMI), exposure and response prevention, at least two combination strategies (including combined SRI and behavior therapy), a MAOI trial, a trial with a novel antidepressant (eg, venlafaxine), and ECT (if depression is present).

Repetitive transcranial magnetic stimulation (rTMS) provides a relatively noninvasive probe of cortical function. In rTMS, a pulsatile high-intensity electromagnetic field emitted from a coil placed against the scalp induces focal electrical currents in the underlying cerebral cortex. Cortical activity can be stimulated or disrupted by rTMS. Although its primary application to date has been investigations of the relationship between regional cortical activity and function in health and disease, some studies suggest rTMS may have therapeutic value in depression and perhaps in OCD. In a preliminary controlled study, Greenberg et al. reported that a single session of rTMS applied to the right prefrontal cortex produced a transient reduction in compulsive urges. It is possible that the anti-OCC effect of rTMS stemmed from its interference with ongoing neuronal activity mediating the compulsive urges. rTMS is not without risk, as seizures have been reported in at least 6 (of more than 250) subjects undergo-
ing the procedure. Local discomfort from activation of scalp musculature and nerves also occurs. Further evaluation of rTMS as an investigatory and therapeutic tool in OCD seems justified.

SUMMARY

Despite an apparently adequate trial with an SRI, a number of patients with OCD experience minimal or no clinical gains. Options in dealing with the SRI-resistant OCD patient include switching to a different SRI, combining another medication (or behavior therapy) with the SRI, considering novel or experimental drug treatments, or employing nonpharmacologic biologic approaches. A discussion of behavior therapy is beyond the scope of this article, but there is reason to believe that, in many cases, an adequate course of behavior therapy may be what the SRI-resistant patient needs most. The main limitations of behavior therapy are shortages of trained therapists and the inability of many patients to comply with treatment.

Unfortunately, none of the SRI-drug combination approaches to treatment-resistant OCD can be viewed as firmly established. In the case of SRI plus lithium or SRI plus buspirone, encouraging open-label reports have been followed up by mostly negative controlled trials. The lack of a mean between-group difference should not completely overshadow the observation that some individual patients do seem to benefit from lithium or buspirone addition. Potential clinical indicators for adding lithium or buspirone to an SRI are, respectively, prominent depressive symptoms or generalized anxiety disorder. The proposed predictor for buspirone needs to be evaluated prospectively in a controlled trial. The combination of fluvoxamine and CMI to capitalize on a drug-drug interaction (ie, elevating plasma concentrations of CMI) deserves further research. Adding a low dose of a conventional neuroleptic (such as haloperidol or pimozide) or a newer agent (such as risperidone) to a selective SRI should be considered in treatment-resistant cases with a comorbid tic disorder even if the tics themselves do not merit pharmacologic treatment. Addition of clonazepam to SRI therapy may be worthy of consideration, but cannot be enthusiastically endorsed until more controlled trials appear. Several reports during a number of years suggest that intravenously administered CMI may have a place in the management of treatment-resistant OCD. ECT may have a role in the severely depressed patient with OCD who has been refractory to pharmacologic and behavioral approaches. The treating physician should be cognizant of current evidence regarding the possible role of stereotactic neurosurgery in severe

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refractory OCD. A proposed algorithm for the medical management of OCD is presented in the figure.

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