Refractory Obsessive-Compulsive Disorder: State-of-the-Art Treatment

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Nonresponse to treatment in obsessive-compulsive disorder is common, associated with substantial impairment, and understudied. Little practical advice is available to clinicians on next-step treatment strategies for patients who have not responded well to 2 trials of selective serotonin reuptake inhibitors (SSRIs). Available options include continuation of SSRI treatment, switching to another SSRI or selective serotonin-norepinephrine reuptake inhibitor, augmenting with atypical neuroleptics or cognitive-behavioral therapy, or utilizing novel treatment approaches. The authors synthesize state-of-the-art treatment and give practical advice for clinicians. *(J Clin Psychiatry 2002;63[suppl 6]:20–29)*

Nonresponse to treatment in obsessive-compulsive disorder (OCD) is common, associated with substantial impairment, and understudied. Little practical advice is available to clinicians on next-step treatment strategies for patients who have not responded well to 2 or more trials of selective serotonin reuptake inhibitors (SSRIs). Much knowledge about OCD comes from multicenter clinical trials, but for those working at specialty OCD centers, there is a constant struggle to find effective treatments for refractory patients, which is clearly an unmet need. Many patients do not have a satisfactory response to the standard treatments, and for these often comorbid and difficult-to-treat patients, few good data exist regarding appropriate and effective treatments. Should these patients be continued on their current medications for longer periods of time? Should they be switched to other SSRIs or selective serotonin-norepinephrine reuptake inhibitors (SNRIs)? Would increasing the dose give a more robust response? Will augmenting with atypical neuroleptics or cognitive-behavioral therapy (CBT) be effective, or should a novel treatment approach be attempted, and are these strategies satisfactory and tolerable for most patients? These are practical questions for which there are few controlled data in large populations with real-life comorbid conditions. In this article, we will consider the issues and strategies related to OCD treatment nonresponders.

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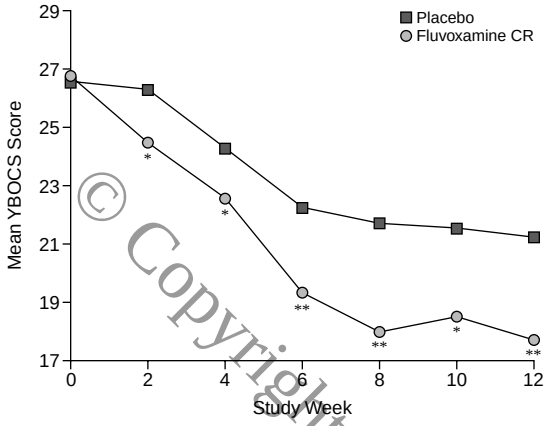
FLUVOXAMINE CONTROLLED RELEASE: A NEW MULTICENTER TRIAL

New findings are available from the most recent multicenter OCD trial with fluvoxamine controlled release (CR).[1] This 12-week, double-blind, flexible-dose, placebo-controlled, parallel-arm, multicenter trial was designed to determine the safety and efficacy of fluvoxamine in a CR formulation in adult outpatients with OCD. Two hundred fifty-three adult outpatients with a primary DSM-IV diagnosis of OCD were randomly assigned to receive 100 to 300

Figure 1. Mean Yale-Brown Obsessive Compulsive Scale (YBOCS) Scores During a 12-Week Study of Fluvoxamine Controlled Release (CR) Versus Placebo in 253 Adult Outpatients With Obsessive-Compulsive Disorder[a]



[a]Data from Hollander et al.[1] Intent-to-treat population.
*p < .050.
**p < .010.

mg/day of fluvoxamine CR (N = 127) or placebo (N = 126) once daily for 12 weeks. Efficacy assessments were the Yale-Brown Obsessive Compulsive Scale (YBOCS), the Clinical Global Impressions-Severity of Illness (CGI-S) score, and the Clinical Global Impressions-Global Improvement (CGI-I) score. Intent-to-treat analysis was used to assess outcome.

Fluvoxamine CR was significantly superior to placebo in decreasing the YBOCS total score beginning as early as week 2, and this early response was sustained at all subsequent visits (Figure 1). At endpoint, there was an 8.5 ± 0.7 (31.7%) drop in the YBOCS total score compared with baseline in the fluvoxamine CR treatment group versus a 5.6 ± 0.7 (21.2%) drop in the placebo group, based on a last-observation-carried-forward (LOCF) algorithm (p = .001). Fluvoxamine CR was also significantly superior to placebo in lowering the severity of illness as measured by the CGI-S and in improving the subjects' condition as measured by the CGI-I. A significantly greater percentage of subjects in the fluvoxamine CR treatment group were responders (CGI-I score of 1 or 2) compared with the placebo group at endpoint. Over 12 weeks, fluvoxamine CR treatment, given once daily, was associated with a statistically significant and clinical relevant reduction in OCD severity.

Of particular interest, the therapeutic effect had a very early onset, starting from week 2. This CR formulation was found to be safe and well tolerated. It allows a higher initial dose, a treatment strategy that might explain the earlier onset of action. Nevertheless, as with all SSRIs, some patients fail to respond to a therapeutic trial, and more work is needed to understand the nature of these nonresponders.

Table 1. Family History of Obsessive-Compulsive Disorder (OCD) and Tics[a]

Family History	Total Sample (N = 274)	Responders (N = 127)	Nonresponders (N = 147)
OCD	39.7%	36.8%	42%
Tics*	4.2%	7.5%	1.6%

[a]Data from Hollander et al.[1]
*p = .024.

CHARACTERIZATION OF NONRESPONDERS: PRELIMINARY RESULTS FROM THE INTERNATIONAL OCD TREATMENT REFRACTORY CONSORTIUM

The large number of nonresponsive patients is difficult to characterize because of ambiguities in diagnostic criteria, the possible existence of subtypes, and the high rate of comorbidity in these patients. The findings of studies of so-called "nonresponsive" cases cannot be generalized because of the lack of an operational definition of nonresponse. Because of the lack of a clear definition for nonresponse, a cumulative body of data on a reasonably homogeneous sample of nonresponders has not been developed. Now available are preliminary findings of the International OCD Treatment Refractory Consortium. The aim of this project is to analyze OCD patients who respond and do not respond to various treatments and determine differences between these groups. The study involved retrospective review of OCD patient records at 8 international sites.[2] Each site was asked to collect data on 25 responders and 25 nonresponders (resistant or refractory) via a questionnaire detailing demographics, specific profile of OCD, treatment history, and responsivity to treatment. The ultimate data collection goal is 450 records. Preliminary results of 274 patients are currently available. Some findings were unexpected and paradoxical: treatment responders had a higher rate of family history of tics (Table 1) and more comorbid impulsive aggressive disorder (Figure 2). Some of the data were as expected: nonresponders had more severe illness (Figure 3), poorer insight (Figure 4), and more comorbid bipolar and eating disorders (see Figure 2). Responders also had a higher incidence of sudden onset of illness (p = .055) and episodic course of illness (p = .000) (Figure 5). No significant differences were noted between responders and nonresponders on age, gender, age at onset, length of illness, or prominent symptom subtypes. Better characterization of the patients who respond and do not respond to various treatments will enable more accurate clustering of patients and help facilitate multisite data collection for future research trials. This study will provide a rich database that can be mined to better understand the nature of treatment nonresponse in real-life OCD patient populations.

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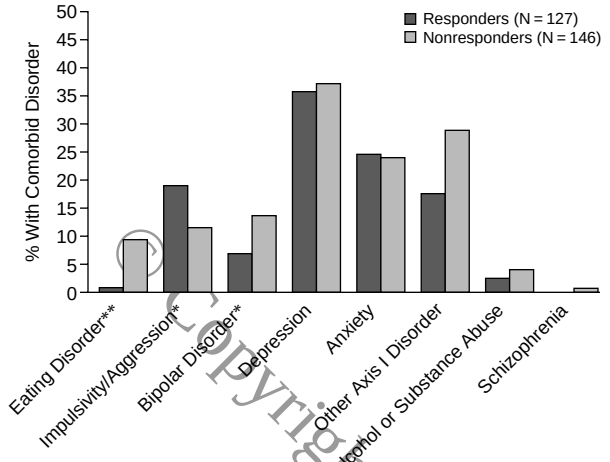
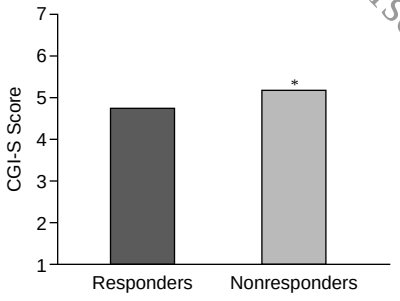
Figure 2. Disorders Comorbid With Obsessive-Compulsive Disorder: Responders Versus Nonresponders[a]



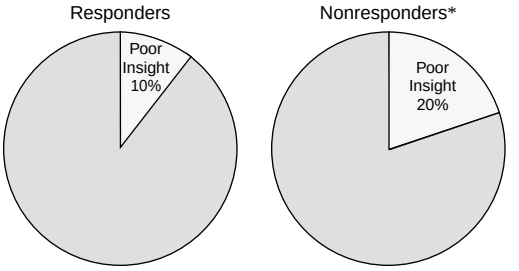
[a]Data from Hollander et al.[2]
*p < .09.
**p < .01.

Figure 3. Mean Clinical Global Impressions-Severity of Illness Scale (CGI-S) Score: Responders Versus Nonresponders[a]



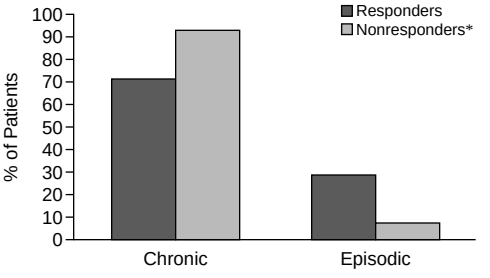
[a]Data from Hollander et al.[2]
*p = .001.

Figure 4. Subtypes of Obsessive-Compulsive Disorder: Poor Insight[a]



[a]Data from Hollander et al.[2]
*p < .025.

Figure 5. Subtypes of Obsessive-Compulsive Disorder: Chronic Versus Episodic[a]



[a]Data from Hollander et al.[2]
*p = .000.

IMAGING AND TREATMENT RESPONSE

A positron emission tomography (PET) study using ^{11}C α–methyl tryptophan (^{11}C-αMT) was designed to elucidate serotonergic mechanisms and treatment response in OCD.[3] One theory of the antiobsessional properties of SSRIs is their ability to enhance serotonergic neurotransmission in distinct brain pathways. Whether other effective treatments in OCD, including CBT, "act" via similar mechanisms is unknown. In this study, PET with an analog of tryptophan, ^{11}C-αMT, was used to measure aspects of serotonin (5-HT) metabolism in OCD prior to, and in response to, long-term treatment with either an SSRI or CBT. The study followed a parallel-group design, with patients being randomly assigned to either sertraline or CBT. PET determination of ^{11}C-αMT plasma-to-brain clearance (K*) was obtained at baseline and after 10 to 12 weeks of continuous treatment. Sixty-minute dynamic PET studies were performed using an ECAT-HR + scanner. All patients underwent a magnetic resonance (MR) examination for PET/MR coregistration. Treatment effects were examined using a semiautomated region of interest (ROI)-based image analysis procedure.

Fourteen OCD patients have completed the study at this time, 8 in the sertraline group (6 men/2 women, mean ± SD age = 33.4 ± 8.5 years, YBOCS score = 22.7 ± 5) and 6 in the CBT group (4 men/2 women, age = 36.2 ± 10 years, YBOCS score = 24.1 ± 5.7). On the basis of a cutoff point of a ≥ 33% decline in YBOCS scores, 5 of 8 sertraline-treated patients and 2 of 6 CBT-treated patients were deemed responders or partial responders to treatment. Six ROI were selected a priori for pretreatment/posttreatment comparisons: dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex, orbitofrontal cortex, anterior cingulate, caudate nucleus, and thalamus. A 3-way analysis of variance identified a treatment (sertraline vs. CBT) by response (response vs. nonresponse) by time (pretreatment vs. posttreatment) interaction (p = .05) for global K*, suggesting a different pattern of change as a function of treatment modality and outcome: ^{11}C-αMT plasma-to-brain

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clearance increased in OCD patients responding to CBT, but not in those responding to sertraline. This effect was in part driven by 1 patient with intractable washing, whose response to CBT was marked, together with a tripling of global K* values at 3 months. The effect of treatments on global K* disappeared on reanalysis with this case omitted as an outlier. Under those conditions (N = 13), ^{11}C-αMT plasma-to-brain clearance at 3 months increased in treatment responders, independent of treatment modality, only in 1/6 ROI, DLPFC ($p < .03$). However, changes in regional K* did not significantly correlate with outcome. The data were approached with the assumption that most of the effects should be in the medication group. Changing state seemed to be most associated with changing biology, and that happened mostly and dramatically in the CBT group. The results suggest that patients who respond have improvement in serotonin synthesis in key brain regions. These intriguing results deserve exploration in future studies.

REVIEW OF TREATMENT OPTIONS FOR NONRESPONDERS

A number of options are available for patients with treatment-refractory OCD.

Behavioral Therapy

In cases of partial or nonresponse, an attempt should be made to combine behavioral therapy with pharmacologic treatments. In cases of nonresponse, family therapy, too, should be suggested, in order to assess the family dynamics and to determine whether a family member is colluding with the patient's disorder (for example, by impeding exposure trials and hence preventing improvement).

SSRIs and Clomipramine

If patients cannot tolerate adequate doses of SSRIs or have not responded to SSRI administered in the upper range of the relevant dose, a trial of clomipramine is recommended (and vice versa). In patients aged 40 years and older, clomipramine should be given after an adequate work-up that includes an electrocardiogram (ECG) and rules out ophthamologic problems (e.g., closed angle glaucoma). Although no fixed-dose studies have been carried out, it seems that high doses of clomipramine are needed in order to attain responses in OCD patients. Titration to these doses should take 1 to 3 weeks. Therapeutic drug monitoring should be performed if possible in order to ascertain blood levels (200–500 ng/mL) for the parent drug plus the desmethyl derivative and to avoid side effects that result from very high (or even toxic) blood levels. If tolerated, a dose of 200 to 300 mg/day is considered efficacious in OCD, and this dose should be administered for 10 weeks before determining lack of response.

Augmentation

Augmentation is called for when there is partial or no response to the above mentioned approaches. Combination of SSRIs (or SRIs) with medications such as risperidone, pindolol, buspirone, lithium, fenfluramine, trazodone, tryptophan, olanzapine, or thyroid hormones has been reported. To date, only 2 augmenting agents have been found to be effective in double-blind studies, i.e., risperidone[4] and pindolol.[5]

Risperidone. Risperidone in small doses—1 to 2 mg twice a day—was found in 1 double-blind study[4] and 3 open-label studies[6–8] to be effective in alleviating obsessive-compulsive symptoms in some partial or nonresponders. The additional benefit was unrelated to whether tic disorder is present.

Pindolol. Pindolol augmentation (2.5 mg of pindolol, 3 times daily) of SSRIs has also been found in a double-blind study[5] to be effective and thus might be placed quite high on the list of augmenting agents. However, it appears to give an extra "push" to partial responders rather than actually turning nonresponders into responders.

Lithium. Several open reports suggest the efficacy of lithium in OCD.[9–11] However, the only double-blind, placebo-controlled study[12] failed to find significant statistical differences between placebo and lithium augmentation.

Buspirone. The value of buspirone augmentation in OCD is unclear, as reports of its efficacy are conflicting.[13–15] If attempted, buspirone is started with doses of 5 mg t.i.d. and advanced as tolerated to a therapeutic dose of 30 to 60 mg/day, usually given in 3 divided doses for a period of 6 weeks.

Clomipramine. An augmentation of SSRIs with clomipramine (or vice versa) is a common practice in nonresponders, although double-blind studies of the efficacy of this approach are lacking. In these cases, the clinician should bear in mind the possible interaction between SSRIs and clomipramine, as the coadministration of SSRIs with tricyclic antidepressants such as clomipramine may lead to a substantial increase in the level of tricyclics in the blood.

Fenfluramine. Fenfluramine releases serotonin into the synapse and blocks the reuptake, thus potentially augmenting the effect of SSRIs by increasing the concentration of serotonin in the synaptic cleft. Fenfluramine augmentation (20–60 mg/day for several weeks)[16] is no longer used since this medication is no longer available.

Trazodone. Several case reports[17,18] describe the efficacy of trazodone for OCD, but a controlled study[19] was terminated prematurely because the investigators had not noticed a response. Doses of 100 to 200 mg/day are recommended.

Tryptophan. L-Tryptophan, the amino acid precursor of serotonin, has been reported to be effective in OCD.[13] However, one should be careful with tryptophan augmentation, due to the safety issue (association between tryptophan and eosinophilia myalgia syndrome). The recommended dose of tryptophan is 2 to 10 g/day.

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Thyroid hormones. L-Triiodothyronine has been reported to be efficacious in open trials as an adjunctive agent SSRI in major depression.[20–23] However, a controlled study did not confirm this agent's efficacy in OCD.[24] The recommended dose is 25 to 50 μg/day.

Olanzapine. Olanzapine is also a viable option for augmentation and is discussed below.

Clozapine. Several open reports have been published concerning a transient exacerbation of OCD symptoms owing to clozapine treatment.[25–27] These reports suggest that, on the basis of the hypersensitivity hypothesis of OCD, chronic treatment might have beneficial effects. However, a study[28] in which clozapine monotherapy was administered to 20 treatment-resistant OCD patients for 10 weeks reported a lack of efficacy.

Other Options

Intravenous clomipramine. Several studies have reported on the efficacy of intravenous clomipramine with intractable OCD.[29–31] This strategy includes daily infusions of clomipramine for 14 days, the maximum dose being 325 mg, or pulse loading of 150 mg on day 1 and 200 mg on day 2 followed, after a 4-day delay, by oral clomipramine.

Monoamine oxidase inhibitors (MAOIs). A placebo-controlled trial[32] of fluoxetine versus phenelzine for OCD provides no evidence to support the use of phenelzine in OCD except possibly for patients with symmetry-related or other atypical obsessions. An earlier controlled, comparative study[33] of clomipramine and clorgiline, a reversible MAO-A inhibitor, also failed to show any beneficial effect of MAOIs. Only one small, controlled study,[34] which compared phenelzine and clomipramine (without placebo), suggests that phenelzine may be effective. Doses of phenelzine up to 90 mg/day should be used for at least 10 weeks.

Clonazepam. Several case reports[35–37] suggest the efficacy of clonazepam as monotherapy and as an augmentation treatment in OCD. This benzodiazepine also has effects on the serotonergic system, thus providing a theoretical explanation for its role in OCD. However, negative results were reported in one controlled study (E.H., unpublished observations, 2002).

Inositol. An improvement in OCD was reported in one double-blind study[38] following 6 to 12 grams of inositol in treatment-refractory OCD patients; a second study reported negative results.[39] Additional studies to resolve this disagreement are indicated.

Clonidine. An α_2-adrenergic agonist, clonidine has been reported to be effective for OCD symptoms in the context of Tourette's disorder.[40] Despite a report of improvement in typical OCD patients with intravenous clonidine[41] and one case report of success[40] with this drug when given alone orally, the range of associated side effects and the lack of controlled studies hinder its use for OCD patients.

Electroconvulsive therapy (ECT). The evidence accumulated so far with regard to ECT is not compelling, and altogether, it seems that the pure antiobsessional effect of ECT is questionable. ECT should probably be reserved for the symptomatic treatment of severely depressed and suicidal OCD patients.

Transcranial magnetic stimulation (TMS). A few cases[42] suggest a potential for use of this technique in OCD. Further studies are needed to clarify technical issues as well as efficacy.

Antiandrogen therapy. One group reported that the antiandrogen cyproterone acetate alleviated OCD symptoms.[43] However, another group's attempt to replicate this finding failed.[40] Further investigations of antiandrogen therapy are warranted.

Neurosurgery. The last resort is neurosurgery. Current operations include anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy, and limbic leucotomy. These procedures are helpful in some patients and are relatively safe. Although well-controlled studies are difficult to perform, several follow-up studies have been published.[40] On the basis of these studies, about 40% to 60% of patients would be expected to receive total or partial benefit from neurosurgery. Some cases, which have benefited only partially from neurosurgery, display a better response to other treatment modalities that were previously ineffective. With the advent of new techniques (i.e., gamma knife[44]), double-blind sham procedures will be possible, making a controlled efficacy study possible.

Special Conditions

If the diagnosis is OCD and a tic disorder, small doses of pimozide[45] or haloperidol[46] in addition to the serotonergic drug are associated with a higher therapeutic response. If a schizophrenic patient has both schizophrenia and OCD, addition of an antiobsessive treatment to the ongoing neuroleptic treatment may be useful.[47] This combination has been associated with somewhat better outcome in such patients who are otherwise difficult to treat. The role of mixed dopaminergic and serotonergic blockers such as risperidone in this subset of patients has not been studied systematically. Given the pharmacologic profile of these medications and some open reports of their efficacy in OCD, the atypical antipsychotics may be worth more study.

AUGMENTATION STRATEGIES FOR NONRESPONDERS

Olanzapine

A placebo-controlled trial of augmentation of SSRI response in refractory OCD used adjunctive olanzapine.[48] Thus far, only conventional neuroleptics and risperidone have been found effective in placebo-controlled augmentation studies for refractory OCD. Olanzapine, an atypical antipsychotic with less likelihood of extrapyramidal side

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effects than typical neuroleptics or risperidone, has shown promise as an adjunctive treatment for SRI-refractory OCD in open trials. This study determined the efficacy of adding olanzapine to SRIs in refractory OCD in a double-blind, placebo-controlled augmentation study. Twenty-six patients meeting DSM-IV criteria for OCD who had not responded to SRIs were randomly assigned to 6 weeks of adjunctive treatment with either 5 to 20 mg/day of olanzapine (N = 13) or placebo (N = 13). Subjects with any other current primary psychiatric diagnosis were excluded. Severity of illness was assessed by the YBOCS and CGI-I, and analysis was conducted using LOCF. Linear regression was used to compare improvement on the YBOCS. The subjects in the olanzapine group had a mean ± SD decrease of 4.7 ± 2.2 in YBOCS score, compared with a mean increase of 0.54 ± 0.36 in the placebo group ($p = .05$). Olanzapine (mean final dose = 11.2 mg/day) was well tolerated. Only 2 subjects (15%) discontinued olanzapine because of side effects, while 5 subjects stopped placebo because of lack of response. Six subjects (46%) in the olanzapine group showed ≥ 25% improvement in YBOCS score, 5 improved at least 35%, and 4 of these were "much improved" on the CGI-I. No subjects in the placebo group met any criteria for response. Adjunctive olanzapine was well tolerated and was significantly superior to placebo in reducing OCD symptoms, indicating that it can be an effective treatment strategy for SRI-refractory OCD. While patients who may not respond to standard treatments may benefit from augmentation strategies such as olanzapine, long-term tolerability issues will need to be explored in future studies.

Olanzapine for Schizophrenia Patients With Nonresponsive OCD

An open-label case series of olanzapine treatment for patients with schizophrenia and refractory OCD was studied recently.[49] About 25% of patients with schizophrenia also have obsessive-compulsive (OC) symptoms. In patients with both schizophrenia and OCD, exacerbation of OC symptoms following treatment with clozapine,[25,50,51] risperidone,[52] and olanzapine[53,54] has been reported. However, in another case report, clozapine reduced OC symptoms.[51] Moreover, other open reports[55–57] suggest that a combination of clozapine and an SSRI reduce OC symptoms in schizophrenia. The data regarding olanzapine and OC symptoms in schizophrenia are conflicting: exacerbation is reported in some[53,54] but not all[58] reports. The open-label case series[49] examined the effect of a combination of olanzapine with antiobsessive medications in 9 patients with comorbid schizophrenia and OCD. The 5 women and 4 men had an age range of 22 to 42 years (mean ± SD = 28.9 ± 6.1). All patients were diagnosed as having schizophrenia and OCD according to DSM-IV criteria. No patient was psychotic at the time of treatment. All 9 patients had completed a trial of at least one SSRI or clomipramine, each for at least 12 weeks with high doses, and all were being treated with antipsychotics at the time of the trial.

Olanzapine augmentation was initiated at a daily dose of 2.5 mg/day and then titrated as tolerated up to 10 mg (mean ± SD final dose = 6.5 ± 2.3 mg/day). Obsessive-compulsive symptoms were assessed every 4 weeks during the 8-week augmentation trial using the YBOCS, the Brief Psychiatric Rating Scale (BPRS), the Global Assessment of Functioning (GAF), and the CGI. Six of 9 patients with both schizophrenia and OCD who had not responded to other antipsychotic medication responded after being switched to olanzapine. The response took place after several weeks of olanzapine treatment. Four of 9 patients were responders, as indicated by a greater than 40% decrease in YBOCS score and a rating of "much improved" or "very much improved" on the CGI scale. These patients also showed significant decrease in BPRS score, and 2 of them showed a significant increase in GAF score. Another 2 subjects were "partial responders," i.e. at least 30% decrease in YBOCS score and rating of "minimally improved" on the CGI scale with no significant change in either BPRS or GAF. The remaining 3 patients were "nonresponders" with no improvement in their OC symptoms nor on any other measure. One patient reported worsening of OC symptoms after 8 weeks of treatment in comparison to her condition when treated with risperidone. The olanzapine dose was 5 mg/day in 6 patients and 10 mg/day in 3 patients. All patients with significant improvement with olanzapine treatment were maintained on that treatment for a 6-month follow-up period. One patient reported worsening of the OC symptoms after 10 months; raising the olanzapine dose to 7.5 mg/day resumed the improvement. Paired t test for all patients with confidence interval of 95% was performed. Improvements in YBOCS and BPRS were significant ($p < .005$ and $p < .05$, respectively). However, change in GAF was not significant ($p < 0.1$). This may raise the question whether OC symptoms and negative symptoms in schizophrenia share the same pathophysiology and therefore respond to the same medication. Olanzapine was well tolerated in this group of patients accustomed to antipsychotics. Sedation was reported by 50% of patients; 2 complained about weight gain. Three patients were treated successfully with olanzapine alone. This case series suggests that olanzapine may be therapeutically effective for some patients with both schizophrenia and OCD who do not respond to a combination of other antipsychotics (both typical and atypical) and SSRIs. Further double-blind investigation of the efficacy of atypical neuroleptics such as olanzapine for the treatment of OC symptoms and OCD in patients with schizophrenia appears warranted.

Gabapentin

Gabapentin augmentation of fluoxetine in OCD and its effects on symptoms and on cortical excitability has been

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studied recently.[59] The γ-aminobutyric acid (GABA) modulator gabapentin was reportedly beneficial as an augmenting agent in a small open study[60] in OCD patients. The preliminary findings require replication, particularly given the history of encouraging case reports and open trials of SRI augmentation with several agents that were followed by controlled trials with negative results. Gabapentin is interesting because of its benign side effect profile and because a therapeutic benefit might potentially result from gabapentin-induced normalization of an excessive cortical excitability in OCD. Increased excitatory responses, together with reduced inhibitory processing, has been reported in OCD patients using paired-pulse transcranial magnetic stimulation (pTMS) as a physiologic probe.[61] Gabapentin has also been reported to enhance cortical inhibition in healthy volunteers,[62] so reduction of abnormally increased cortical excitability in OCD after gabapentin treatment is plausible.

In the study of gabapentin plus fluoxetine in OCD, OCD patients with a minimum YBOCS score of 16, despite at least 3 months of fluoxetine monotherapy, received added gabapentin for a total of 6 weeks, titrated to a maximum and stable daily dose of 3600 mg over the first 2 weeks, or placebo in a randomized, crossover design. Preliminary data analysis indicated no improvement in YBOCS scores at the end of the gabapentin arm compared with placebo treatment. Preliminary analysis also suggested no enhancement of inhibitory processing on pTMS after chronic gabapentin treatment in the subset of patients undergoing pTMS. The results fail to confirm the hypothesis that gabapentin augmentation of fluoxetine in OCD patients is effective in reducing core OC symptoms and further suggest that the addition of chronic gabapentin treatment did not enhance intracortical inhibitory processing in this patient group (B.D.G., unpublished observations).

SWITCHING STRATEGIES FOR NONRESPONDERS

Venlafaxine

Venlafaxine, an SNRI similar to clomipramine but lacking the anticholinergic, antihistaminic, and α-adrenergic blocking effects, has been studied in the treatment of OCD.[63–65] However, all such studies lasted only 8 weeks, and no studies have included treatment-resistant OCD patients. A 12-week, single-blind study of venlafaxine versus clomipramine in acute-phase treatment (study 1) and a 12-week, single-blind study of venlafaxine versus clomipramine and citalopram in patients unresponsive to at least 2 trials of SSRIs other than citalopram (study 2) were conducted recently.[66]

Study 1 included 73 OCD patients (DSM-IV; YBOCS score ≥ 16) referred to the Anxiety and Mood Disorders Unit of the University of Turin, Italy. Subjects with a current comorbid major depressive episode; a lifetime comorbidity with schizophrenia, organic mental disorder, or substance abuse/dependence; or a current medical condition that would contraindicate the use of venlafaxine or who were currently on clomipramine treatment were excluded from the study. All patients were drug free for at least 2 months prior to study enrollment. Participants were randomly assigned to receive 225 to 350 mg/day of venlafaxine (26 patients) or 150 to 225 mg/day of clomipramine (47 patients) for 12 weeks, with dosage adjustments according to tolerability and response. Efficacy measures were the YBOCS and the CGI, which were completed at baseline and every 4 weeks. Responders were defined as those patients with an improvement ≥ 35% on YBOCS from baseline and a CGI score ≤ 2. An investigator who was blind with respect to medication administered rating scales independently. Moreover, patients were instructed not to reveal to this investigator their current treatment. Twenty-five patients in the venlafaxine group and 40 in the clomipramine group completed the 12-week trial. Two different statistical methods evaluated responders: a visitwise analysis and an LOCF analysis. At the end of the 12 weeks, responder rates were 36% for venlafaxine (9 of 25) versus 50% for clomipramine (20 of 40) according to the visitwise analysis and 34.6% (9 of 26) for venlafaxine versus 42.5% (20 of 47) for clomipramine according to the LOCF analysis, with no statistically significant difference found between the 2 drugs. Patients in the venlafaxine group reported significantly fewer side effects compared with patients taking clomipramine. These results indicate that venlafaxine may be as efficacious as clomipramine in the acute treatment of OCD but with fewer side effects and confirm and extend previous reports.

In study 2, 28 OCD patients (DSM-IV; YBOCS score ≥ 16) unresponsive to at least 2 documented trials with SSRIs (fluoxetine, fluvoxamine, paroxetine, or sertraline) at adequate dosage and for at least 12 weeks (full dosage) were included. All patients were drug free for at least 2 months prior to study enrollment. Participants were randomly assigned to receive venlafaxine, 225–350 mg/day (8 patients); clomipramine, 150–225 mg/day (11 patients); or citalopram, 40–60 mg/day (9 patients) for 12 weeks, with dosage adjustments according to tolerability and response. Efficacy measures were the YBOCS and the CGI, completed at baseline and every 4 weeks. Responders were defined as those with an improvement ≥ 35% on YBOCS with respect to baseline and a CGI score ≤ 2. Seven patients in the venlafaxine group, 8 in the clomipramine group, and 7 in the citalopram group completed the 12-week trial. The visitwise responder results were venlafaxine, 3 of 7 (42.8%); clomipramine, 3 of 8 (37.5%); and citalopram, 1 of 7 (14.3%). LOCF analysis responder results were venlafaxine, 3 of 8 (37.5%); clomipramine, 3 of 11 (27.3%); and citalopram, 1 of 9 (11.1%). Results indicate that after 2 failed SSRI trials, clinicians should consider switching OCD patients to clomipramine or venlafaxine. Given the better tolerability of venlafaxine with respect to clomipra-

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mine and the initial reports of an antiobsessional property of this agent, a switch to venlafaxine appears to be a reasonable alternative. The results should be interpreted with caution and need to be replicated in controlled studies.

Switching SSRIs: Citalopram and Fluvoxamine

In OCD patients who failed trials with other SSRIs, switching to another SSRI may elicit a good response. A study[67] on the use of citalopram at a fixed daily dose of 40 mg in 18 refractory OCD patients included patients who had been treated with different drugs at other dosages for adequate times and were considered to be treatment refractory. Beginning 4 weeks after starting citalopram treatment, a significant decrease in the YBOCS total score was observed. This improvement continued with time (mean ± SD baseline YBOCS score = 29.7 ± 5.7; week 4 YBOCS score = 22.0 ± 6.8; week 16 YBOCS score = 15.1 ± 7.6 [$p \leq .01$]). Fourteen of 18 patients improved with citalopram treatment, and the treatment was well tolerated. Shifting from one SSRI to another may be effective because, although all these drugs block the serotonin transporter, their receptor profiles are different, which may explain the specificity of response. A study[67] on the use of fluvoxamine in OCD used a fixed daily dose of 300 mg in 8 patients with OCD. Patients were titrated up to 300 mg/day from 100 mg/day within 10 days, since faster titration may prevent the onset of side effects. Seven patients were "very much improved" as measured by CGI at the end of the fourth week of treatment, and this response increased with time. These data with regard to switching were unexpected, since the earlier literature suggested that perhaps only 25% of patients get a good response on switching. Further systematic research is indicated.

NOVEL APPROACHES

Oral Morphine

A placebo-controlled, double-blind study[68] of oral morphine for treatment-resistant OCD hypothesized that once-weekly oral morphine would benefit patients with treatment-resistant OCD. Case reports and open-label trials have documented response of treatment-resistant OCD patients to oral morphine[69] and tramadol,[70,71] a μ-opioid receptor mixed agonist/antagonist with modest serotonin and norepinephrine reuptake activity. In this study of oral morphine, patients were recruited from an OCD clinic. Inclusion criteria were a history of OCD for longer than 3 years, failed trials of adequate doses of at least 2 SSRIs, and a YBOCS score greater than 21. Patients could continue current medications, which were required to be stable for 2 months before the trial. Exclusion criteria were history of narcotic, benzodiazepine, or alcohol abuse or a medical condition in which narcotics were contraindicated. Patients underwent a screening evaluation including the YBOCS and were then randomly assigned to double-blind, 2-week blocks of morphine sulfate starting at 30 mg per week, lorazepam starting at 1 mg per week, or placebo in a crossover design. The medication was administered in the clinic. One week after the first administration, the YBOCS evaluation was repeated, side effects assessed, and a decision made to increase, decrease, or maintain the medication dosage for week 2. Lorazepam was included to reduce the chance that side effects such as drowsiness would compromise the blind.

Results are available for the first 8 patients. The mean ± SD baseline YBOCS score was 28.3 ± 5.9. The mean YBOCS score for the week after the highest morphine dose taken (mean = 37.5 + 8.0 mg) was 21.0 ± 6.1. Three of the 8 patients had a ≥ 40% decrease in YBOCS score, and 1 had a 29% decrease. The mean decrease in YBOCS score was 26.2% ± 14.5%. No patient's YBOCS score increased in the week after morphine administration. In contrast, in the week after the highest lorazepam dose (mean = 1.6 ± 0.5 mg), the mean YBOCS score was 24.8 ± 5.3. Two patients had a decrease of greater than 25% (27% and 29%), and 2 had a small increase in YBOCS score (1–2 points). The mean decrease in YBOCS score was 11.3% ± 14.4%.

In the placebo group, the mean YBOCS score in the week after the highest dose was 25.3 ± 4.9, a decrease of 10.1% ± 11.4%. No placebo patient achieved a YBOCS decrease of ≥ 25%, and 1 patient's YBOCS score increased by 3 points. The percentage of decrease after double-blind morphine treatment was statistically significant compared with the decrease after placebo (Student t test, $p = .006$); the decrease after lorazepam treatment was not statistically different from placebo (Student t test, $p = .71$). A single dose of oral morphine is well tolerated and can substantially ameliorate OCD symptoms in some patients during the week after the dose. This finding suggests that other neurotransmitter and peptide systems may play a role, perhaps through their effects on other neurotransmitter systems. Systematic long-term follow-up is needed to determine whether the early responses persist over time and whether intermittent oral morphine is a tolerable treatment approach over time.

Sumatriptan and 5-HT_{1D} Receptor Agonists

After considering the effects of 5-HT receptor agonists with different binding profiles on the symptoms of OCD, it may be hypothesized that the 5-HT_{1D} receptor is implicated in the pathophysiology of OCD. A 5-day, randomized, double-blind, placebo-controlled trial[72] of oral sumatriptan, 100 mg/day, in medication-free adults with OCD studied whether sumatriptan, a 5-HT_{1D} agonist, would diminish 5-HT release, thereby worsening OCD symptoms. By beginning to desensitize 5-HT_{1D} receptors, sumatriptan given prior to treatment may promote a faster response or an increased likelihood of response to subsequent treatment with an SSRI. The results showed that

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the OCD symptoms of 5 sumatriptan subjects worsened as measured by the YBOCS (mean ± SD decrease = 17.6% ± 14.6%), which was significant when compared with the slight symptom decrease in the 5 placebo subjects (mean ± SD decrease in YBOCS score = 5.2% ± 4.9%, $p < .015$). The sumatriptan group did not exhibit a faster response or greater likelihood of response to a 90-day, open-label trial of paroxetine. Longer-term studies of the effects of 5-HT_{1D} agonists on OCD symptoms are indicated, and zolmitriptan, a potent 5-HT_{1D} receptor agonist with better penetration of the blood-brain barrier, may be a preferred challenge agent.

Anterior Gamma Capsulotomy

Anterior gamma capsulotomy has also been thought to be an effective treatment for intractable OCD, which is defined as at least 5 years of intensive medication and behavioral therapies. In 2 recent studies,[73] patients received bilateral single lesions in the anterior limb of the internal capsule or bilateral double lesions placed just ventral to the initial lesion in the coronal plane. The single lesion was ineffective and not associated with a placebo response. The double lesion resulted in clinical improvement in 38% to 50% of patients in the 2 studies. There were no decrements in cognitive performance or adverse personality changes observed, but a few patients had side effects such as headache or edema.

Overall, the degree of improvement, which is considered to be therapeutically meaningful in this severely affected population, appears faster with the double shot than the single shot repeated procedure. The issue of risks and benefits from a gamma knife approach versus deep-brain stimulation should be addressed in future research.

SUMMARY

New data and practical advice on the management of treatment-refractory OCD are continually forthcoming. This common, disabling, and understudied condition provides a challenge to even the most skilled clinician. New multicenter trial data have emerged, and ongoing collaborations are necessary in order to achieve better characterization of and improve treatment strategies for the resistant patient. Hopefully, this information will spur further research and help provide guidance for the informed clinician.

Drug names: citalopram (Celexa), clonazepam (Klonopin and others), clonidine (Catapres and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), gabapentin (Neurontin), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), paroxetine (Paxil), phenelzine (Nardil), pimozide (Orap), risperidone (Risperdal), sertraline (Zoloft), sumatriptan (Imitrex), venlafaxine (Effexor).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, buspirone, citalopram, clonazepam, clonidine, clorgiline, fenfluramine, gabapentin, haloperidol, lithium, olanzapine, phenelzine, pindolol, risperidone, sumatriptan, tramadol, trazodone, tryptophan, and zolmitriptan are not approved by the U.S. Food and Drug Administration for the treatment of obsessive-compulsive disorder.

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