Update on Pharmacologic Management of OCD: Agents and Augmentation

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A preponderance of patients with obsessive-compulsive disorder (OCD) experience little or no improvement in their symptoms when treated with serotonin reuptake inhibitors (SRIs). It is hypothesized that SRI-refractory patients may have altered serotonin neurotransmission different from patients responsive to SRIs, or that they may have abnormalities in their dopamine function. When drugs affecting serotonin function (e.g., tryptophan, fenfluramine, lithium, buspirone) are added to SRI therapy in SRI-refractory patients, results are mixed and not consistently encouraging. However, when drugs affecting dopamine function (e.g., pimozide, haloperidol, risperidone) are added to SRI therapy in SRI-refractory OCD patients, individuals with either a personal history or family history of tics experience a reduction in their symptoms. *(J Clin Psychiatry 1997;58[suppl 12]:11–17)*

Despite significant advances in pharmacologic treatment with potent serotonin (5-hydroxytryptamine [5-HT]) reuptake inhibitors (SRIs), as many as 40% to 60% of obsessive-compulsive disorder (OCD) patients are clinically unchanged after an adequate trial with these agents.[1] Moreover, for most patients who respond to SRIs, the improvement is incomplete. In many large-scale clinical trials, for example, a 25% to 35% decrease in severity of obsessive-compulsive (OC) symptoms as measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[2,3] corresponds to a categorical treatment response. While this modest degree of reduction in symptom severity may enhance the patient's functional capacity, few patients become asymptomatic.

The lack of significant improvement in OC symptoms in the large group of SRI-refractory OCD patients suggests that the disorder may be neurobiologically heterogeneous and that many patients may require pharmacologic treatments other than SRI monotherapy for maximal symptom control. It is conceivable that SRI-refractory patients may have alterations in 5-HT neurotransmission that are different from those in patients who are responsive to SRIs. Alternatively, these patients may have OCD as a result of abnormalities in neurochemical systems different from or in addition to those involving 5-HT (e.g., dopamine [DA]).[4,5]

SRI PLUS DRUGS AFFECTING SEROTONIN FUNCTION

A number of agents affecting 5-HT function, including tryptophan,[6,7] fenfluramine,[8] lithium,[7,9–15] and buspirone,[16–18] have been investigated for their potential to decrease OC symptoms when added to ongoing treatment with SRIs (Table 1).

Adding Tryptophan

Rasmussen reported in a case study that the addition of tryptophan, the amino acid precursor of 5-HT, to ongoing clomipramine treatment led to a significant improvement in OC symptoms.[7] However, others have found no improvement with this approach,[6] and no controlled studies evaluating the efficacy of adding tryptophan to ongoing SRI therapy in patients with OCD have been published. Adverse neurologic reactions resembling the 5-HT syndrome observed in laboratory animals have been reported when tryptophan is used in combination with fluoxetine.[19] In addition, oral tryptophan is currently unavailable in the United States because of evidence linking some preparations with the eosinophilia myalgia syndrome.[20,21]

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Table 1. Controlled Trials of Serotonergic Agents in SRI-Refractory OCD

Study	N	SRI	Dose (mg)	Results
Lithium				
McDougle et al (1991)[12]	30	Fluvoxamine	300	Negative
Pigott et al (1991)[13]	16	Clomipramine	250	Negative
Buspirone				
McDougle et al (1993)[16]	33	Fluvoxamine	300	Negative
Grady et al (1993)[18]	13	Fluoxetine	80	Negative
Pigott et al (1992)[17]	14	Clomipramine	250	Negative

Adding Fenfluramine

Hollander et al.[8] observed that the addition of open-label *d*, *l*-fenfluramine, an indirect 5-HT agonist, to ongoing SRI treatment led to improvement in OC symptoms in six (86%) of seven patients. Subsequently, two clomipramine-treated patients were reported to improve following addition of *d*-fenfluramine,[22] which is believed to have more specific effects on 5-HT transport and release than the racemic mixture but which is unavailable in the United States.

Some studies in laboratory animals have suggested that fenfluramine may be neurotoxic.[23] However, the lack of direct evidence that fenfluramine is toxic to 5-HT neurons in humans may reflect the difficulty in determining subtle neurologic changes upon routine clinical examination. The preadministration of an SRI appears to prevent fenfluramine-induced 5-HT neurotoxicity by blocking entry of fenfluramine into 5-HT nerve terminals.[24] Thus, with regard to 5-HT neurotoxicity, the combined administration of an SRI and fenfluramine may be safer than the administration of fenfluramine alone. However, no controlled studies have been published that indicate that fenfluramine addition is efficacious in SRI-refractory OCD.

Adding Lithium

Lithium has been hypothesized to potentiate antidepressant-induced increases in 5-HT neurotransmission by enhancing presynaptic 5-HT release in some areas of the brain.[25] Based on the serotonin hypothesis of OCD[26] and the efficacy of lithium augmentation in refractory major depression,[27] adding lithium to ongoing antidepressants has been investigated as a potential treatment approach in patients with OCD.

In individual cases, lithium has been reported to augment the antiobsessional effect of chronic treatment with imipramine,[15] clomipramine,[7,10,11] desipramine,[9] and doxepin[11] in patients with OCD. Also, the addition of open-label lithium to ongoing fluoxetine treatment reportedly led to an improvement in OC symptoms in three (75%) of four patients with OCD.[14]

In contrast, no significant improvement in OC symptoms has been shown in controlled studies of lithium addition in patients with OCD. Following 4 weeks of double-blind lithium augmentation of ongoing clomipramine treatment in 16 OCD patients who had demonstrated a partial response to clomipramine, Pigott et al.[13] observed no further reduction in OC symptoms. In a study by McDougle et al.,[12] 2- and 4-week double-blind, placebo-controlled trials of lithium augmentation of ongoing fluvoxamine treatment were conducted in 20 and 10 patients with primary OCD, respectively, who had not responded to fluvoxamine monotherapy. Two weeks of double-blind lithium augmentation produced a small but statistically significant reduction in OC symptoms, although most patients did not have a clinically meaningful response. Furthermore, during the subsequent 4-week double-blind, placebo-controlled trial, there was no significant statistical or clinical improvement in OC symptoms. Only 18% and 0% of the patients met criteria for a response to lithium augmentation during the 2- and 4-week treatment trials, respectively. Based on these controlled studies, the addition of lithium to the treatment of patients with SRI-refractory OCD does not appear to achieve the rate and quality of response that are typically observed with this strategy in antidepressant-resistant depression.[27]

Adding Buspirone

Buspirone is a 5-HT_{1A} receptor partial agonist that, following chronic treatment, has been shown in preclinical studies to enhance 5-HT neurotransmission.[28] Two open-label studies have investigated the use of buspirone as an adjunct to ongoing SRI treatment of patients with OCD. Markovitz et al.[29] and Jenike et al.[30] reported that the addition of buspirone to ongoing fluoxetine treatment led to a greater reduction of OC symptoms than did treatment with fluoxetine alone. Also, an open-label case study described positive results with this approach in an 11-year-old girl with OCD and comorbid major depression.[31]

Results from controlled studies of buspirone addition in OCD patients refractory to SRI monotherapy, however, have not corroborated these initial reports. Pigott et al.[17] found that the addition of buspirone, up to 60 mg/day for 10 weeks, to the treatment protocols of 14 patients whose symptoms had partially improved following at least 3 months of clomipramine did not produce significant further improvement. Similarly, in a double-blind, placebo-controlled investigation of 6 weeks of buspirone addition to ongoing fluvoxamine treatment, McDougle et al.[16] found buspirone (up to 60 mg/day) no better than placebo in reducing OC, depressive, or anxiety symptoms in OCD patients. On the basis of conservative treatment response criteria, 2 (11%) of the 19 patients who received 6 weeks of buspirone addition to ongoing fluvoxamine demonstrated a response (1 marked, 1 partial), whereas 2 (14%) of the 14 patients treated with placebo showed a response (1 marked, 1 partial). Negative results have also been reported from a controlled study evaluating the efficacy of buspirone addition in fluoxetine-refractory OCD patients.[18]

In light of the serotonin hypothesis of OCD,[26] a better response to lithium and buspirone addition to ongoing SRI treatment might have been predicted in these controlled treatment studies. Chaput and colleagues[32] have suggested that chronic administration of SRIs enhances net 5-HT neurotransmission by desensitizing inhibitory presynaptic 5-HT autoreceptors. Combining this presumed action of SRIs with lithium's facilitatory effect on presynaptic 5-HT neurons,[25] the net effect would be to enhance 5-HT neurotransmission.[33] The chronic administration of buspirone has also been shown in preclinical studies to enhance 5-HT neurotransmission.[28] The facilitation of 5-HT function by a drug, however, may not constitute efficacious treatment of OCD. As Blier and de Montigny[34] observed, the lack of response to lithium augmentation in OCD patients may be related to the differential regional effects of lithium on 5-HT release in the central nervous system. Similarly, although buspirone administration may be affecting 5-HT function, this activity may not be occurring in areas of the brain hypothesized to be involved in the pathophysiology of OCD.[35]

Because of the heterogeneous clinical presentation of OCD patients,[36] the inconsistent treatment outcome with SRI monotherapy,[1] and the variation in behavioral and neurochemical responses to neuropharmacologic probes of 5-HT function,[37,38] it would be simplistic to assume that abnormalities in the 5-HT system alone could fully explain the complex neurobiological processes mediating OC symptoms. Several lines of evidence suggest, for example, that the brain DA system may contribute significantly to the pathophysiology and treatment of OC phenomena.[4]

SRI PLUS DRUGS AFFECTING DOPAMINE FUNCTION

Although the role of 5-HT in the treatment of OCD has been established, evidence from preclinical and clinical investigations implicates DA in the mediation of some forms of OCD.[4] Considerable preclinical data suggest the existence of significant anatomic and functional interactions between 5-HT and DA systems in the brain, particularly in the basal ganglia.[39,40]

Relationship Between Some Forms of OCD and Tourette's Disorder

Tourette's disorder is a chronic neuropsychiatric disorder of childhood onset that is characterized by multiple motor and phonic tics that wax and wane in severity.[41] In addition to tics, many patients with Tourette's disorder have comorbid OCD. However, although the tics of Tourette's disorder are often reduced with DA receptor antagonists,[42] comorbid OC symptoms are typically resistant to treatment with neuroleptic alone.[5] Similarly, the frequency and intensity of OC symptoms in patients with a principal diagnosis of OCD are rarely decreased with neuroleptic monotherapy.[4,5]

While the etiology of Tourette's disorder remains unknown, neurobiological,[43] pharmacologic,[42] neuroanatomic,[44] brain-imaging,[45] and genetic[46] data implicate the DA system, in part, in the pathobiology of Tourette's disorder. It may be that some forms of OCD, particularly those comorbid with chronic tic disorders, are associated with abnormal DA function.[4]

To our knowledge, there have been no published controlled trials of DA receptor antagonist monotherapy in the treatment of OCD as it is currently defined in DSM-IV. Most experienced clinicians agree that, in general, DA receptor antagonists alone are not effective in the treatment of the core symptoms of OCD.

Adding DA Receptor Antagonists

In light of the phenomenologic,[47,48] neurobiological,[49] and genetic[50] overlap between some forms of OCD and chronic tic disorders, and because of the extensive preclinical literature documenting functionally coupled interactions between the 5-HT and DA systems in the brain,[39,40] some investigators have been pursuing SRI/DA receptor antagonist combination treatment strategies in subgroups of OCD patients with SRI-refractory symptoms.

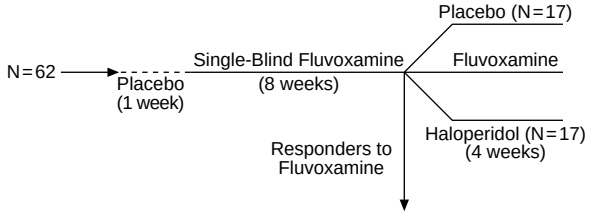
Adding Pimozide

In an open case series by our group at Yale,[51] neuroleptic therapy, primarily pimozide, was added to ongoing treatment in 17 nonpsychotic OCD patients unresponsive to fluvoxamine with or without lithium. These cases were reviewed by a rater blind to treatment outcome to determine whether comorbid chronic tic disorders or schizotypal personality disorder was associated with a positive response to pimozide addition. According to stringent criteria, 9 (53%) of 17 patients were judged responders to this combination treatment strategy. A concurrent diagnosis of chronic tics or schizotypal personality disorder was associated with a positive response to the addition of pimozide. Seven (88%) of the eight patients with these comorbid diagnoses were responders, whereas only two (22%) of the nine patients without these comorbid diagnoses were responders.

Adding Haloperidol

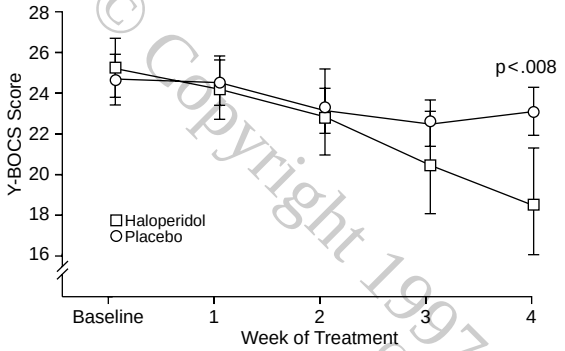
In a double-blind, placebo-controlled study in OCD patients with and without comorbid chronic tic disorders, the DA receptor antagonist haloperidol (mean ± SD dose = 6.2 ± 3.0 mg/day) was significantly more effective than placebo when added to ongoing fluvoxamine treatment in OCD patients unimproved with fluvoxamine monotherapy[52] (Figure 1). The superiority of haloperidol over placebo in reducing the severity of OC symptoms was shown with the Y-BOCS. There was significant im-

Figure 1. Haloperidol Addition in Fluvoxamine-Refractory OCD: Study Design*



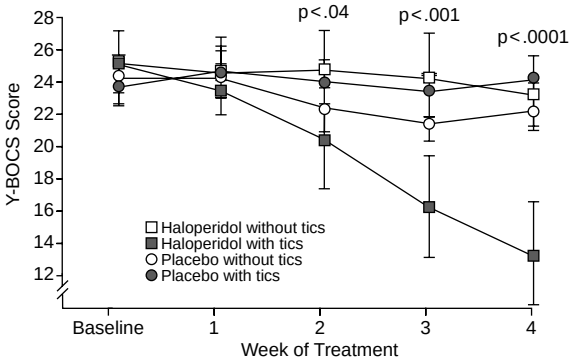
*Based on reference 52.

Figure 2. Response to Haloperidol*



*Reprinted with permission from reference 52.

Figure 3. Response to Haloperidol in Patients With and Without Tics*



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provement in OC symptoms beginning at Week 3 in the fluvoxamine-haloperidol–treated group. In contrast, there was no significant change in OC symptom severity at any time during the 4 weeks of placebo addition to ongoing fluvoxamine treatment. Based on conservative treatment response criteria, 11 (65%) of the 17 patients randomly assigned to receive haloperidol were rated as responders after 4 weeks of treatment, compared with none of 17 patients who received placebo (Figure 2). Furthermore, as hypothesized, those OCD patients with a concurrent chronic tic disorder, such as Tourette's disorder, demonstrated a preferential response to the fluvoxamine-haloperidol combination treatment strategy (Figure 3). In fact, all eight patients with comorbid chronic tic disorders responded to double-blind haloperidol addition to ongoing fluvoxamine treatment. These results suggest that OCD patients with a comorbid chronic tic disorder may represent a valid and reliable subtype of OCD requiring conjoint SRI/DA receptor antagonist therapy for effective symptom reduction. Moreover, these drug-response data indicate that both the brain 5-HT and DA systems may contribute to the treatment response and, perhaps, the pathophysiology of this tic-related subtype of OCD. While the relationship between OCD with comorbid chronic tic disorders and response to neuroleptic addition was substantiated in this study, it was not possible to make definitive conclusions about the usefulness of this treatment strategy in OCD patients with comorbid schizotypal personality disorder because our sample included only two such patients.

Although neuroleptic addition was found to be effective in reducing OC symptoms in a significant number of patients, it should not be used indiscriminately in the treatment of OCD, as these patients often require prolonged pharmacotherapy for continued symptom reduction. Because of the substantial risks of tardive dyskinesia, adequate trials of at least two selective SRIs and clomipramine should be completed before neuroleptic addition is considered. Furthermore, a time-limited trial of neuroleptic addition should be attempted, with reassessment of the risk/benefit ratio of ongoing neuroleptic treatment at regular intervals.

Based on our clinical experience since completion of the double-blind, placebo-controlled study of haloperidol addition described above, we now typically begin haloperidol 0.5 mg/day with subsequent increases every 4 to 7 days to a maximum of 2 to 4 mg/day, as clinically indicated. The recent development of alternative drug treatments that modulate DA transmission without the high risks of toxic extrapyramidal side effects (e.g., clozapine and risperidone) may prove useful in some patients with OCD (see below).

Clozapine Monotherapy

Clozapine is an atypical neuroleptic that is effective in patients with treatment-resistant schizophrenia.[53] The drug's ability to block 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, and DA D4 > D3 > D2 = D1 receptors has been proposed as its mechanism of action. Based on clozapine's neurochemical profile and on the efficacy of combined SRI/DA receptor antagonist treatment in some forms of SRI-refractory OCD,[52] our group recently completed a 10-week systematic investigation of clozapine monotherapy in adults with treatment-resistant OCD.[54] Ten of 12 patients who entered the study completed the 10-week trial of clozapine. Two patients discontinued the trial prematurely because of

sedation (100 mg/day for 3 weeks) and hypotension (125 mg/day for 2 weeks), respectively. The mean ± SD dose of clozapine in the 10 completers was 462.5 ± 93.7 mg/day. Clozapine was not associated with statistically significant improvement in scores on the Y-BOCS, the Y-BOCS obsession subscale, the Y-BOCS compulsion subscale, the Hamilton Rating Scale for Depression, and the Clinical Global Impression global improvement item. None of the 10 patients met criteria for treatment response. Two patients who had comorbid chronic motor tic disorder showed no significant reduction in tics. Side effects included sedation (N = 6), constipation (N = 1), hypotension (N = 2), weight gain (N = 1), nocturnal enuresis (N = 2), nausea (N = 1), and dizziness (N = 1). The results of this systematic investigation suggest that clozapine monotherapy is not an effective intervention for most adult patients with treatment-refractory OCD. The role of clozapine addition in SRI-refractory OCD remains undetermined.

Adding Risperidone

Risperidone is a highly potent and selective 5-HT_2 receptor antagonist that also acts as an antagonist at the α_1, histamine-1, DA D_2, and α_2 receptor sites.[55] It has no peripheral or central anticholinergic activity, nor does it have significant interactions with opioid, benzodiazepine, substance P, or neurotensin receptors.[56] Thus, its side effects appear to be much more tolerable and safer than those of DA D_2 receptor antagonists currently used to treat SRI-refractory OCD, such as haloperidol and pimozide. Our group recently described our initial experience in adding risperidone to ongoing fluvoxamine treatment in three patients with SRI-refractory OCD.[57] Preliminary results from a 6-week, double-blind, placebo-controlled trial, in which low dosages (0.5–2.0 mg/day) of risperidone were given to SRI-refractory OCD patients following 12 weeks of SRI therapy, have been encouraging. Treatment response was rapid and well maintained, and side effects were minimal. The following case exemplifies our preliminary observations:

Case report. Ms. A, a 52-year-old married woman, first developed OC symptoms at the age of 20 years. Her primary symptoms consisted of contamination and sexual obsessions and repeating and washing compulsions. At the age of 23, she developed a secondary major depressive episode. Her OC symptoms persisted without significant improvement until her presentation to our clinic 32 years after the onset of her OCD. Ms. A had received numerous somatic treatments prior to entering our program. At the age of 25, she had a course of electroconvulsive therapy without improvement. She received subsequent treatment with tranylcypromine 60 mg/day, phenelzine 60 mg/day plus lithium carbonate 900 mg/day, phenelzine plus lithium and fluphenazine 10 mg/day, clomipramine 250 mg/day with clonazepam 1 mg/day, clomipramine plus lithium, clomipramine plus haloperidol 1 mg/day, clozapine 600 mg/day, fluvoxamine 300 mg/day, and fluvoxamine plus desipramine 150 mg/day plus 6 months of in-home exposure and response prevention behavior therapy, with no improvement in her OC symptoms.

Risperidone 1 mg/day was added to fluvoxamine 250 mg/day, and, within 2 weeks, Ms. A reported a marked reduction in her level of anxiety, improved mood, and increased ability to resist performing compulsions. She showered unassisted for the first time in 3 years, ate dinner with her husband in a restaurant for the first time in 8 years, had sex with her husband for the first time in 6 years, began assisting her housekeeper in cleaning her home, and began to look for volunteer work. Four weeks following risperidone addition, Ms. A had a reduction in her Y-BOCS score from 31 to 11. She has retained this treatment response, with mild sedation being the only side effect. Interestingly, Ms. A had a family history of chronic tics. The two other OCD patients in this preliminary report who had a similar treatment response had comorbid schizotypal personality disorder and body dysmorphic disorder, respectively.

The addition of risperidone to ongoing SRI therapy may also be an effective treatment for some children with SRI-refractory OCD. In a recently completed open-label trial, we found that risperidone in doses of 1.5 to 2.5 mg/day was effective in reducing children's Y-BOCS scores by 16%, 100%, and 30% when added to ongoing paroxetine 60 mg/day, sertraline 100 mg/day, and paroxetine 30 mg/day, respectively, in children with chronic tic disorders with comorbid OCD.[58]

SUMMARY

To date, two primary lines of approach have been taken in the development of pharmacologic treatments for the SRI-refractory OCD patient. Controlled studies of the first approach—adding drugs that further enhance 5-HT function, such as lithium and buspirone—have not yielded consistently encouraging results. The second major line of investigation has involved the addition of DA receptor antagonists, such as haloperidol and pimozide, to the treatment regimen of SRI-refractory OCD patients. This combination treatment strategy has been shown to be effective in reducing OC symptoms primarily in SRI-refractory patients who have comorbid personal or family histories of chronic tics. Preliminary reports describing the effectiveness of risperidone addition to SRIs are encouraging, as this drug has been associated with fewer acute and chronic extrapyramidal side effects than typical neuroleptics. Controlled studies of risperidone addition are needed in children and adults with SRI-refractory OCD. Finally, the addition of other drugs with demonstrated efficacy for

reducing tics, such as the α_2-adrenoceptor agonists clonidine[59] and possibly guanfacine,[60] may be worthy of study as adjuncts to SRIs in the treatment of tic-related forms of OCD.

Drug names: buspirone (BuSpar), clomipramine (Anafranil), clonazepam (Klonopin), clonidine (Catapres), clozapine (Clozaril), desipramine (Norpramin and others), doxepin (Sinequan and others), fenfluramine (Pondimin), fluoxetine (Prozac), fluphenazine (Prolixin and others), fluvoxamine (Luvox), guanfacine (Tenex and others), haloperidol (Haldol and others), imipramine (Tofranil and others), paroxetine (Paxil), phenelzine (Nardil), pimozide (Orap), risperidone (Risperdal), sertraline (Zoloft), tranylcypromine (Parnate).

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