Ondansetron Augmentation in Treatment-Resistant Obsessive-Compulsive Disorder: A Preliminary, Single-Blind, Prospective Study

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Abstract

Background: Serotonin and dopamine neuronal systems have been implicated in the modulation of obsessive-compulsive disorder (OCD) symptoms. About 40% of OCD patients do not respond to first-line selective serotonin reuptake inhibitor (SSRI) treatment; among those, dopamine blocker augmentation has been reported to improve the rate of response by an additional one-third. Given that serotonin 5-HT₃ receptors are indirect inhibitors of cortico-mesolimbic dopamine release, augmentation with the 5-HT₃ receptor antagonist ondansetron in combination with SSRIs and antipsychotics has potential efficacy in treatment-resistant OCD patients.

Objective: To assess the efficacy and tolerability of ondansetron in combination with SSRIs and antipsychotics in patients with treatment-resistant OCD.

Method: In total, 14 patients with a DSM-IV diagnosis of OCD, who were treatment resistant and receiving stable treatment with SSRIs and antipsychotic augmentation, entered a 12-week, single-blind trial of ondansetron. The drug was initiated at a dosage of 0.25 mg twice daily for 6 weeks and was then titrated to 0.5 mg twice daily for 6 weeks.

Results: Of the 14 patients, nine (64.3%) experienced a treatment response (≥25% reduction in the Yale-Brown Obsessive Compulsive Scale [YBOCS] score and a Clinical Global Impressions-Improvement [CGI-I] score of 1 or 2) at 12 weeks. The average reduction in YBOCS-rated symptoms for the whole group was 23.2%. None of the treated patients experienced symptom exacerbation or significant adverse effects.

Conclusion: These results suggest that low-dose ondansetron may have promise as an augmentation strategy for some patients with OCD resistant to SSRIs and antipsychotic augmentation, but further controlled trials are required.

Trial registration number (ClinicalTrials.gov): NCT00796497
Background

Selective serotonin reuptake inhibitors (SSRIs) are considered the most effective and well-established pharmacotherapy for the treatment of obsessive-compulsive disorder (OCD). However, 40–60% of OCD patients do not respond adequately to SSRI medications, and an even greater proportion of patients do not experience complete remission of their symptoms. Several augmentation strategies have been proposed for the treatment of resistant and refractory OCD. One of the most popular strategies involves the addition of low-dose dopamine antagonists to SSRI medications. While the notion that SSRIs possess antiobsessional efficacy has led to the ‘serotonin hypothesis of OCD’ during the last 2 decades, there is now growing evidence that the dopamine system may be involved in OCD as well. In fact, in addition to the indirect evidence provided by treatment efficacy with antipsychotic augmentation strategies, the role of a corticostriatal ‘hyperdopaminergic state’ in OCD repetitive behaviours has also been suggested by experiments in animal models, pharmacological challenges (cocaine, methylphenidate, apomorphine), neuroimaging and genetic findings (reviewed in Denys et al.). Since typical antipsychotics and clozapine monotherapy are considered ineffective as OCD treatment options, and since only one-third of treatment-refractory OCD patients show a meaningful treatment response to antipsychotic augmentation, the search for other pharmacological strategies based on the interaction between the serotonergic and dopaminergic systems is growing. Serotonin 5-HT3 receptors are co-localized with GABA interneurons in the ventral tegmental area, and they act indirectly by inhibiting cortico-mesolimbic dopamine release. It is of interest with regard to OCD treatment that 5-HT3 receptor antagonists like ondansetron were shown to reduce the reinforcing effects of a variety of abused drugs, including alcohol and amphetamines. This phenomenon was presumably explained by the attenuation of suprabasal cortico-mesolimbic dopamine release following the withdrawal from cocaine use. Furthermore, in humans, the 5-HT3 receptor antagonist ondansetron was also shown to inhibit increased right orbitofrontal cortex neuronal activation and cerebral blood flow in recently withdrawn cocaine addicts. An increased neural activation of this region has been consistently reported in OCD. Antagonism of 5-HT3 receptors is thought to be a contributing factor in the therapeutic effect of atypical antipsychotic agents. This mechanism may also explain the suggested efficacy of ondansetron in treatment-resistant schizophrenia.

Taken together, these possible mechanisms of action suggest the potential efficacy of ondansetron augmentation in SSRI- and antipsychotic-resistant OCD. To the best of our knowledge, no studies have reported an investigation of this association in treatment-resistant OCD. Previously, Hewlett and colleagues demonstrated, in a pilot trial, that ondansetron monotherapy was effective in three of eight non-resistant OCD patients. However, the sample did not include treatment-resistant patients or an association with antipsychotic medications.

The aims of this study were to assess the efficacy and tolerability of this pharmacological combination in treatment-resistant OCD, to identify future directions regarding 5-HT3 receptors and dopamine interactions in OCD and to determine whether different antipsychotic pharmacodynamic profiles influence treatment responses.

Methods

Patients and Treatment

Between March 2008 and November 2008, at the Institute for Neuroscience in Florence, Italy, we enrolled 14 adults aged 18–55 years with a diagnosis of treatment-resistant OCD. Resistance was defined as a Yale-Brown Obsessive Compulsive Scale (YBOCS) score ≥20 after ≥12 weeks of treatment with an established effective dose of an SSSI or clomipramine and ≥10 weeks of augmentation treatment with antipsychotics (risperidone at a dosage of at least 2 mg/day; quetiapine at a dosage of at least 250 mg/day).
least 150 mg/day,\(^{26}\) olanzapine at a dosage of at least 5 mg/day,\(^{27}\) haloperidol titrated to a dosage of at least 10 mg/day,\(^{28}\) or aripiprazole at a dosage of at least 10 mg/day\(^{29}\). Specifically, the stage of resistance of our sample was stage VII, according to the classification of resistance reported by Pallanti et al.\(^{23}\). This implies the failure of at least three SSRI trials (including clomipramine), cognitive-behavioural therapy and other classes of medication (e.g. benzodiazepines, mood stabilizers or antipsychotics).

The investigators established all diagnoses utilizing a structured interview, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I).\(^{30}\) Potential subjects with a history of alcohol or substance abuse, current severe depressive symptoms, bipolar disorder, panic disorder, schizophrenia or other psychiatric conditions, heart disease, arrhythmia, liver problems (including cirrhosis), seizures, glaucoma or serious medical diseases were excluded. We also excluded patients with hoarding as their only OCD symptom as well as women of child-bearing age not using a medically acceptable contraceptive method.

After being fully informed about the study and signing an informed consent approved by the Internal Institutional Review Board (Florence, Italy), patients received ondansetron hydrochloride (oral solution) at a dosage of 0.25 mg twice daily for 6 weeks followed by 0.5 mg twice daily for 6 weeks, for a total observation period of 12 weeks. Given the augmentation nature of our investigation, in this sample of patients receiving SSRI and antipsychotic treatment and therefore already vulnerable to the development of gastrointestinal adverse effects, the dosage of ondansetron was kept as low as possible. Furthermore, a gradually increased dosage allowed us to study higher tolerable dosages of ondansetron augmentation while avoiding constipation, an adverse effect reported previously at higher dosages,\(^{21}\) which may be an important source of discomfort for patients with OCD. A similar approach was previously used by Johnson et al.\(^{31}\). Individual dose titrations instead of a fixed-dose regimen have been recently suggested as a more appropriate strategy for achieving optimal results with 5-HT\(_3\) receptor antagonists for CNS-related indications.\(^{32}\)

Assessments

Patients were seen at a screening visit, followed by a baseline visit after 2 weeks. At this time, inclusion/exclusion criteria, OCD symptoms, co-morbid symptoms and vital signs were assessed. We administered the YBOCS and Montgomery-Åsberg Depression Rating Scale (MADRS)\(^{33}\) at the screening and baseline visits and repeated these assessments at each follow-up visit at 6-week intervals, along with the Clinical Global Impressions-Improvement (CGI-I) rating\(^{34}\) and an unpublished Drug Effect scale. The Drug Effect scale asked subjects to rate “How anxious are you now?” on a scale ranging from zero (“not at all”) to ten (“the most anxious I have ever been”). Similar rating questions were “Have you experienced an onset or an increase in the frequency of headaches?”, “Have you experienced an onset or an increase in the frequency of fatigue?” and “Have you experienced an onset or an increase in the frequency of constipation?”, along with similar questions regarding other common ondansetron adverse effects (e.g. diarrhoea, urinary retention, itching and dizziness). Furthermore, each evening during the first week of study medication, a study psychiatrist called the subject to inquire about major or unexpected adverse effects (e.g. chest pain, an unexplained skin rash or tremors). We utilized criteria suggested by Mittmann and colleagues\(^{35}\) to classify subjects as having mild depression (MADRS scores of 9–17) or at least moderate depression (MADRS scores ≥18). Subjects with MADRS scores ≥18 were excluded. Ratings were determined by an investigator who was blind to the treatment condition of the patients.

Statistical Analysis

Given the small sample size, mean changes from the baseline for the rating scales were tested with a non-parametric method based on ranks (Wilcoxon signed-rank test) using a two-tailed significance level of \(p \leq 0.05\). Relationships among rated and demographic variables were
tested with Spearman's rank correlation tests using a two-tailed significance level of p ≤ 0.05. We controlled for the effects of age, baseline OCD severity and duration of illness by stratifying through the Mantel-Haenszel $\chi^2$ test. This test permitted a comparison within each stratum (by sex, age, baseline severity and duration of illness) of the number of individuals observed to respond with the expected number in this category if there were no difference in the rates between the responders and non-responders. Similarly, given the differences of ondansetron bioavailability at different body mass indices, we adjusted the results for body mass index.

Results

We enrolled a pre-planned total of 14 patients in the study. All patients were Caucasian (six women and eight men) with a mean (± SD) age of 42.2 (± 10.8) years (range 19–55 years), and they had a mean illness duration of 14.1 (± 4.07) years (range 3–26 years). An additional 20 individuals who were screened were not enrolled for the following reasons: six patients, after hearing details of the study, were not interested; and 14 were not eligible (nine had exclusionary co-morbid conditions; three had inadequate anti-OCD medication dose/duration; and two had insufficient OCD severity). The subjects' clinical characteristics at baseline are summarized in table I.

At the end of the 6th week, 2 (14.3%) of the 14 OCD patients met the YBOCS criteria for 'treatment response' (reduction of ≥25%).[23] The baseline treatment for both of these patients was citalopram (40 mg daily) plus risperidone (2 mg daily). The average YBOCS score change for the whole group at 6 weeks was a 16% decrease (range: 0% change to 31% decrease), and this change was statistically significant (Sum of Ranks = 91; $z = -3.18$; p < 0.001) [figure 1]. None of the 14 subjects experienced significant adverse effects or worsening of OCD symptoms.

The YBOCS score continued to improve from the 6th until the 12th week. At the endpoint, 9 of the 14 patients (64.3%) reached the criteria for 'treatment response' (YBOCS score decrease of ≥25% and a CGI-I score of 1 or 2 [very much or much improved]) [figure 2].[23] One subject, who was undergoing treatment with citalopram (40 mg/day) and risperidone (2 mg/day), experienced a YBOCS score decrease of ≥35%. Three female and six male patients were treatment responders. The baseline SSRI and antipsychotic treatments for the nine adjunctive ondansetron responder patients and for the non-responders are listed in table I.

The average YBOCS score change for the whole group at the end of the 12 weeks was a 23.2% decrease (range: 3.2% increase to 37.4% decrease). The improved YBOCS scores at the 12th week were still significantly different from the scores at the baseline (Sum of Ranks = 105; $z = -3.03$; p = 0.001) [figure 1]. One subject experienced a slight worsening of OCD symptoms from week 11 until week 12, in association with a gastrointestinal infection.

Spearman's non-parametric test did not show any significant correlations between the percentage change in YBOCS scores and other demographic or clinical variables. Mann-Whitney U comparisons showed no significant differences between responders and non-responders with regard to demographic variables such as age (U = 22.00; z = -0.66; exact p = 0.6), body mass index (U = 19.00; z = -1.54; exact p = 0.147) or duration of illness (U = 16.5; z = -0.81; exact p = 0.699) or clinical variables such as baseline YBOCS (U = 11.00; z = -1.54; exact p = 0.122), CGI-I (U = 16.00; z = -0.91; exact p = 0.438) or MADRS (U = 19; z = -0.47; exact p = 0.699) values. The mean MADRS scores did not change significantly from the baseline to the end of week 12.

Furthermore, the Mantel-Haenszel $\chi^2$ test showed no effect on the outcome stratified by sex (Mantel-Haenszel = 0.103; degrees of freedom [df] = 1; p = 0.74), baseline severity (Mantel-Haenszel = 1.156; df = 1; p = 0.28), duration of illness (Mantel-Haenszel = 0.007; df = 1; p = 0.93), age (Mantel-Haenszel = 0.00; df = 1; p = 0.100) or body mass index (Mantel-Haenszel = 0.506; df = 1; p = 0.45). Therefore, there did not appear to be evidence of a possible role of demographic or clinical variables in the ondansetron response.
Ondansetron in Treatment-Resistant OCD

Table I. Baseline clinical characteristics and subsequent clinical measures in responder and non-responder obsessive-compulsive disorder (OCD) subjects receiving ondansetron (n = 14)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responder (n = 9)</th>
<th>Non-responder (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>3 female; 6 male</td>
<td>3 female; 2 male</td>
</tr>
<tr>
<td><strong>Age, y [mean (SD)]</strong></td>
<td>41.8 (11.1)</td>
<td>42.8 (11.4)</td>
</tr>
<tr>
<td><strong>Duration of OCD, y [mean (SD)]</strong></td>
<td>14.8 (5.3)</td>
<td>12.8 (3.7)</td>
</tr>
<tr>
<td><strong>Body mass index [mean (SD)]</strong></td>
<td>23.0 (5.8)</td>
<td>21.8 (1.4)</td>
</tr>
<tr>
<td><strong>Baseline score [mean (SD)]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YBOCS</td>
<td>29.5 (6.4)</td>
<td>24.4 (4.5)</td>
</tr>
<tr>
<td>CGI-I</td>
<td>4.8 (0.7)</td>
<td>5.2 (1.3)</td>
</tr>
<tr>
<td>MADRS</td>
<td>7.0 (2.3)</td>
<td>7.8 (3.6)</td>
</tr>
<tr>
<td><strong>End of 6th week score [mean (SD)]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YBOCS</td>
<td>22.6 (4.2)</td>
<td>22.8 (3.8)</td>
</tr>
<tr>
<td>CGI-I</td>
<td>3.4 (1.6)</td>
<td>4.6 (1.5)</td>
</tr>
<tr>
<td>MADRS</td>
<td>6.7 (2.4)</td>
<td>8.0 (4.0)</td>
</tr>
<tr>
<td><strong>End of 12th week score [mean (SD)]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YBOCS</td>
<td>20.8 (4.1)</td>
<td>21.4 (6.1)</td>
</tr>
<tr>
<td>CGI-I</td>
<td>2.3 (1.2)</td>
<td>4.8 (1.3)</td>
</tr>
<tr>
<td>MADRS</td>
<td>6.8 (2.0)</td>
<td>7.6 (3.8)</td>
</tr>
<tr>
<td><strong>Treatments (patient number: drug name and dosage in mg/day)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3: CIT 40 + RISP 2</td>
<td>1: FLUV 250 + HAL 10</td>
<td></td>
</tr>
<tr>
<td>5: FLUV 250 + HAL 10</td>
<td>2: PAR 40 + ARIP 15</td>
<td></td>
</tr>
<tr>
<td>6: FLUV 250 + RISP 2</td>
<td>4: FLUV 250 + QUET 200^b</td>
<td></td>
</tr>
<tr>
<td>7: PAR 40 + RISP 2</td>
<td>9: CIT 40 + QUET 200^b</td>
<td></td>
</tr>
<tr>
<td>8: PAR 40 + ARIP 15</td>
<td>14: PAR 40 + RISP 2</td>
<td></td>
</tr>
<tr>
<td>10: FLUV 250 + QUET 200^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11: CIT 40 + RISP 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12: CIT 60 + RISP 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13: PAR 40 + RISP 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Selective serotonin reuptake inhibitor (SSRI) dosages are the maximum tolerable dosages after antipsychotic augmentation.

b A dosage of 200 mg/day of quetiapine is less than the dosage (300 mg/day) that separated from placebo in placebo-controlled augmentation trials in OCD, because it is better tolerated by individual patients.

ARIP = aripiprazole; CGI-I = Clinical Global Impressions-Improvement scale;^34 CIT = citalopram; FLUV = fluvoxamine; HAL = haloperidol; MADRS = Montgomery-Asberg Depression Rating Scale;^33 PAR = paroxetine; QUET = quetiapine; RISP = risperidone; YBOCS = Yale-Brown Obsessive Compulsive Scale.^32

Adverse effects throughout the study were mild to moderate and included decreased appetite (two patients for the first 2 weeks of treatment) and headache (two patients for the first 2 weeks of treatment). One patient reported a mild increase in anxiety levels that lasted only one night. No changes in mean pulse rate or mean blood pressure were observed. No patients reported constipation.

**Discussion**

The study results suggest that ondansetron may be an effective adjunctive treatment in OCD patients resistant to SSRI plus antipsychotic therapy. OCD symptoms, measured with the YBOCS, were significantly reduced at 12 weeks. Of this sample of 14 treatment-resistant patients, 64% experienced an additional reduction of ≥25% in their YBOCS score, and the sample as a whole experienced a significant reduction in symptoms, as assessed by the YBOCS severity score, of 16% at week 6 and 23% at week 12 as a result of ondansetron augmentation treatment (figure 1).

This is the first prospective, single-blind, pilot trial that demonstrates the efficacy of ondansetron augmentation in treatment-resistant OCD patients receiving an SSRI plus antipsychotic treatment. A previous open-label, uncontrolled ondansetron monotherapy study reported a
similar average YBOCS score reduction of 28% in a small sample of non-treatment-resistant OCD patients. In this trial, we ruled out the possibility that symptom reduction may be attributed to improvements in other psychopathological features, because we included only patients without any psychiatric co-morbidity as assessed by a psychiatric interview and the SCID I.

The potential efficacy of a serotonergic antagonist like ondansetron in OCD poses an apparent contradiction with the well documented efficacy of SSRIs in OCD treatment, as highlighted by Hewlett et al. Consistent with the potential efficacy of a serotonergic antagonist agent, it has been proposed that SSRI efficacy in OCD may be based on the reduction of 5-HT2c receptor sensitivity due to chronic SSRI stimulation. This possible mechanism may also explain the slow onset of efficacy and the higher SSRI dose needed in OCD. Furthermore, atypical antipsychotics were reported to block 5-HT2a/2c receptors as well, consistent with the alternative hypothesis of SSRI anti-obsessional efficacy.

Another possible mechanism of serotonergic antagonist anti-obsessional efficacy involves dopaminergic inhibition by 5-HT3 receptor blockade. 5-HT3 receptor antagonists partially inhibit the morphine-induced stimulation of dopamine release in the nucleus accumbens as well as corresponding behavioural activation (e.g. grooming, locomotion, rearing and sniffing) in rats. Of note, behaviours, such as grooming, that are induced by κ-opioid receptor stimulation are considered to offer an animal model of OCD and stereotyped behaviours. The pathway of dopamine system inhibition by 5-HT3 receptor antagonism is not fully understood. The cell bodies of the mesolimbic dopamine system are localized in the ventral tegmental area (VTA), and this brain region has been shown to contain high levels of serotonin and to have high-affinity serotonin uptake sites. The mechanism of action of morphine has been shown to involve the inhibition of GABA-ergic neurons exerting tonic inhibition on the dopamine neurons in the VTA via GABA_A receptor activation. The site of action of 5-HT3 receptor antagonists on this morphine-induced action is also most likely to be situated in this brain region; the local injection of 5-HT3 receptor antagonists into the VTA caused an almost complete reversal of the action of morphine, whereas application into the nucleus accumbens was ineffective. Therefore, the following mechanism has been suggested as a possible explanation of the inhibitory effect of 5-HT3 receptor antagonists on the morphine-induced stimulation of mesolimbic dopamine
release and function: the inhibition of 5-HT<sub>3</sub> receptor function increases GABA release, which, in turn, inhibits the mesolimbic dopamine system.

A less extensively investigated hypothesis suggests that 5-HT<sub>3</sub> receptor antagonists are able to modulate the dopaminergic system through nicotinic acetylcholine receptor (nAChR) antagonism. nAChRs are selectively expressed in dopamine neurons and participate in cholinergic transmission. Preclinical and in vivo studies have reported that nAChRs modulate dopaminergic transmission."^"^"^"^"^*^"^*^*"^*^"^*^* Within this neurotransmitter receptor family, 5-HT<sub>3</sub> receptors are more similar to nAChRs, sharing up to 30% sequence homology."^*^*"^*"^* Experimental evidence indicates that select nAChR ligands cross-react with 5-HT<sub>3</sub> receptors as either agonists or antagonists."^*^* Thus, 5-HT<sub>3</sub> receptors seem to participate in physiological effects previously thought to be specific to nAChRs."^*^* Limitations of this study include the non-randomized, single-blind, pilot nature of the design, the relatively small number of patients and the lack of use of the maximum ondansetron dosage. In a study by Hewlett et al."^*^* employing an ondansetron dosage of 3 mg/day, most of the patients reported constipation. Given the nature of our investigation, in a sample of patients taking SSRI and antipsychotic treatment and therefore already vulnerable to the development of gastrointestinal adverse effects, the dosage was kept low. None of our patients experienced significant or lasting adverse effects, likely due to the very low dosage and slow titration of the medication. Similar to previous studies of substance dependence treatment,"^*^* the dosage of 1 mg/day divided for twice-daily administration (approximately 5% of the minimum dose recommended for emesis and nausea treatment"^*^* was reached after 6 weeks and maintained until the 12th week.

The preliminary nature of this study does not allow for a determination of whether our findings were due to the effect of ondansetron itself, the effect of ondansetron augmentation of SSRIs or the effect of antipsychotic therapy. To the best of our knowledge, there are currently no data regarding the anti-obsessional properties of ondansetron augmentation in SSRI monotherapy and therefore we must be cautious in the interpretation of our findings. We cannot rule out the possibility that symptom improvement was due to late-onset antipsychotic augmentation of SSRIs. However, the improvement was seen in the second half of the trial, so it is unlikely that this improvement is attributable to the stable dosage of antipsychotic treatment. Furthermore, the lack of response to antipsychotic augmentation after at least 10 weeks makes a role for antipsychotic augmentation unlikely in the response process. Moreover, two responder patients experienced a worsening of symptoms after discontinuation of ondansetron and asked to resume taking the medication. A discontinuation study should be performed to ensure that symptom improvement was due to ondansetron and not to a delayed antipsychotic effect. Finally, inconsistencies between antipsychotic medications make the interpretation of the results difficult.

**Conclusion**

In our pilot study, ondansetron augmentation showed potential efficacy and was well tolerated in patients with treatment-resistant OCD when given at a low dosage and with slow titration. Future research is needed to confirm this observation via placebo-controlled acute, long-term maintenance, and discontinuation studies with larger patient numbers.

**Acknowledgements**

Funding for this study was provided in part by Transcept Pharmaceuticals, Inc., Pt. Richmond, California, USA. Drs Hollander and Pallanti have served as consultants to Transcept Pharmaceuticals, Inc. Dr Singh is an employee of Transcept Pharmaceuticals, Inc. Drs Bernardi and Antonini have no conflicts of interest to report. Dr Bernardi's current affiliation is Department of Psychiatry, Columbia University, New York, NY, USA. Dr Hollander's current affiliation is Department of Psychiatry, Montefiore Medical Center, University Hospital of Albert Einstein College of Medicine, Bronx, NY, USA.
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