Pilot Trial of Ondansetron in the Treatment of 8 Patients With Obsessive-Compulsive Disorder

William A. Hewlett, M.D., Ph.D.; Sabine P. Schmid, M.A.; and Ronald M. Salomon, M.D.

Background: Serotonin (5-HT) neuronal systems have been implicated in the modulation of obsessive-compulsive disorder (OCD) symptoms. 5-HT_3 receptor antagonists have been found to act as anxiolytics in selected animal models of anxiety; in particular, those involving an element of risk assessment. Since the compulsions of OCD are frequently triggered by an abnormal perception of risk, a pilot study was initiated to determine whether the 5-HT_3 receptor antagonist ondansetron might have efficacy in the treatment of OCD.

Method: Eight medication-free subjects with a DSM-IV diagnosis of OCD and a Yale-Brown Obsessive Compulsive Scale (YBOCS) score ≥ 16 entered an 8-week open-label trial of ondansetron at a fixed dose of 1 mg 3 times daily in a study conducted between February and October 1998.

Results: Six subjects completed the trial. Three subjects (37%) achieved a clinically significant response (≥ 35% reduction in YBOCS score). For these subjects, the average reduction in YBOCS-rated symptoms was 55%. In aggregate, the 8 patients exhibited a 28% reduction in YBOCS-rated symptoms over the course of the trial. The medication was well tolerated.

Conclusion: These results suggest that low-dose ondansetron may have promise as a monotherapy for some patients suffering from OCD.

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Corresponding author and reprints: William A. Hewlett, M.D., Ph.D., Departments of Psychiatry and Pharmacology, Vanderbilt University School of Medicine, A-2209 MCN, Nashville, TN 37232 (e-mail: OCD/TS@vanderbilt.edu).

At one time labeled *Folie de Doubt* (madness of doubt), obsessive-compulsive disorder (OCD) is a psychiatric illness characterized by an inappropriate dreadful doubt and is associated with repetitive behaviors performed to reduce that aversive experience. Individuals with OCD frequently have an unrealistic sense of dreadful risk should their compulsions not be performed. Although OCD is classified as an anxiety disorder, classic benzodiazepines that are effective in treating generalized anxiety symptoms (e.g., diazepam) have no benefit in the treatment of OCD.[1]

Two common forms of treatment are effective in reducing the symptoms of OCD. The first, behavior therapy, involves inducing patients to expose themselves to conditions that trigger their aberrant perceptions of risk, and persuading them to suppress their urges to carry out the compulsive behaviors. While behavior therapy can be effective in reducing symptoms, a sizable minority of patients (approximately 30%) are unwilling to risk exposing themselves to their most feared circumstances and thus cannot be effectively treated with this technique.[2,3]

The second form of treatment involves the use of serotonin reuptake inhibitors (SRIs) such as clomipramine,[4] fluoxetine,[5] sertraline,[6] paroxetine,[7] fluvoxamine,[8] and citalopram.[9] These medications have reduced symptoms by 20%[8] to 39%[4] in randomized placebo-controlled trials (for review see Greist et al.[10]); however, up to 12 weeks of treatment is required to determine treatment response,[11] and 40%[8] to 57%[4] of patients do not experience clinically significant improvement on treatment with these medications. Given this marginal treatment response rate, and a lifetime prevalence of OCD estimated at 1.5% to 2.5%[12] of the population, it is clear that substantial numbers of patients are not effectively treated. A better understanding of the pathophysiology of OCD is needed to develop more effective treatments.

It has been observed that medications having primary benefits in treating OCD appear to enhance serotonergic neuronal interactions. While SRIs are effective in treating OCD, desipramine, a tricyclic antidepressant that is highly selective for the noradrenergic transport protein over the serotonin transporter, is ineffective in treating OCD symptoms.[13] Other medications that have been reported as monotherapies to treat OCD, including clonaze-

pam,[14] venlafaxine,[15] high-dose trazodone,[16] and inositol,[17] also mimic aspects of serotonergic neurotransmission.[18–21] As yet there is little understanding of how serotonergic medications might act to reduce OCD symptoms.

It is known that chronic treatment with SRIs will ultimately augment synaptic concentrations of serotonin, increasing postsynaptic interactions of serotonin with its receptors.[22] Such interactions are complex in that there are as many as 14 different serotonin receptor subtypes[23] with independent brain regional distributions. Selective activation of different subtypes can have different effects on anxiety-related behaviors in animal models. While 5-HT_{1A} activation has been associated with anxiolytic actions,[24] 5-HT_3 receptor activation has been found to increase anxiety-like behavior in animal models.[25,26] By contrast, administration of 5-HT_3 receptor antagonists has been found to reduce anxiety-related behaviors in animal models (for review see Costall and Naylor[27]).

5-HT_3 receptor antagonists have particular efficacy in models in which animals choose to expose themselves to uncertain risk[28] (for review see Jones and Piper[29]). They are less effective or ineffective in models associated with punished responding.[29] Our group has demonstrated that the potent 5-HT_3-selective antagonist DAIZAC[30] behaves as an anxiolytic in the mouse elevated plus-maze model of anxiety.[28] Treatment with this agent is associated with decreases in passive avoidance of the open arm of the maze, without effects on active avoidance behavior on that arm. Given that 5-HT_3 antagonism may reduce perception of uncertain risk and that the aberrant perception of risk is a fundamental source of symptomatology in OCD, we considered the possibility that 5-HT_3 antagonists might have benefit in the treatment of OCD symptoms.

Ondansetron is a 5-HT_3 antagonist that is approved for human use in the treatment of postsurgical and antineoplastic drug-induced nausea and emesis in doses ranging from 20 to 45 mg daily. In human psychiatric populations, low-dose ondansetron (1–6 mg daily) has been utilized in trials for the treatment of alcohol dependence,[31] benzodiazepine withdrawal,[32] schizophrenia,[33] and Tourette disorder,[34] as well as generalized anxiety disorder, social phobia, and panic disorder, with mixed results (for review see Ye et al.).[35] No systematic trials of ondansetron in the treatment of OCD have been reported. We hypothesized, given the effect of 5-HT_3 antagonists on risk-related models of anxiety, that ondansetron might have efficacy in the treatment of OCD. We report here the results of an open trial of ondansetron treatment in 8 subjects with a DSM-IV diagnosis of OCD.

METHOD

Subjects were recruited through newspaper advertising and screened by telephone interview for symptoms of OCD. Eligible candidates between the ages of 18 and 60 years were invited to undergo further screening including the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I),[36] the Yale-Brown Obsessive Compulsive Scale (YBOCS),[37] the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II),[38] a medical history, physical examination, and laboratory screening. The SCID-I and SCID-II interviews included research criteria for putative disorders listed in Appendix B of the DSM-IV (e.g., binge eating disorder, passive aggressive personality disorder). When subjects met research criteria for such a diagnosis, that diagnosis was included in the patient's case summary.

Exclusion criteria included DSM-IV diagnoses of schizophrenia, schizoaffective disorder, organic mental disorder, bipolar disorder, Tourette disorder, current substance dependence or abuse, and current major depressive episode preceding the onset of OCD. Individuals deemed to be a danger to self or others and those requiring treatment with psychotropic drugs, undergoing concomitant behavior therapy, or having significant cardiovascular, hepatic, renal, neurologic, gastrointestinal, pulmonary, hematologic, or systemic disease were also excluded. Inclusion criteria included a DSM-IV diagnosis of OCD, a score of at least 16 on the YBOCS, and an absence of central nervous system–active medications for 5 medication half-lives or a minimum of 2 weeks.

Eight subjects, 5 male and 3 female, aged 31 to 47 years, meeting full inclusion and exclusion criteria, gave Institutional Review Board–approved informed consent and were admitted to the study, which was conducted between February and October 1998. Primary OCD symptoms, age at onset, outcomes of previous medication treatments, and current and past psychiatric diagnoses for each subject are summarized in Table 1. All participants received ondansetron tablets, starting at a dose of 1 mg daily and ramping up to a dose of 1 mg t.i.d. during the first week. This was followed by 7 weeks' treatment at a fixed dose of 1 mg t.i.d. Somatic conditions coinciding with ondansetron treatment are summarized in Table 2. Subjects were subsequently tapered from the medication over a 1-week period. Weekly psychiatric ratings, including the YBOCS, the 21-item Hamilton Rating Scale for Depression (HAM-D),[39] and the Hamilton Rating Scale for Anxiety (HAM-A),[40] were performed with biweekly clinic interviews and phone evaluations on alternating weeks. OCD clinical severity was rated by means of the YBOCS Global Severity rating. Clinical improvement was also rated weekly by means of the YBOCS Global Improvement item (YBOCS GI), measuring improvement in OCD symptoms from the baseline condition with scores ranging from 0 (very much worse) to 6 (very much better). A follow-up interview was conducted 1 week after the taper. Last observation measures were carried forward and used as end-of-treatment ratings for subjects dropping out of the protocol.

Table 1. Subject Entry Information

Case No.	Age (y)/ Sex	Age at Onset, y	OCD Symptoms	Past OCD Medications, Treatment (daily dose, duration; response)	Concurrent (or past) Diagnoses and Associated Symptoms
1	31/M	13	Contamination; decontaminate	No past medication	PTSD (past), tic-like mannerisms
2	42/M	27	Doubt/symmetry; check/arrange	Fluoxetine (40 mg, 3–4 mo; none), sertraline (100 mg, 6 mo; none)	GAD, obsessive-compulsive PD
3	31/M	18	Contamination; decontaminate	Fluoxetine (50 mg, 7 mo; some), sertraline (50 mg, 3 wk; none/minimal), fluvoxamine (150 mg, 11 wk; none/minimal), clomipramine (not known, 1 wk; none/minimal), buspirone[a] (none/minimal), nefazodone[a] (none/minimal), inositol[a] (none/minimal), mirtazapine[a] (none/minimal), bupropion[a] (none/minimal), St John's wort[a] (none/minimal), kava kava[a] (none/minimal), 5-HTP[a] (none/minimal)	Passive-aggressive PD[b]
4	32/F	7–8	Aggressive/sexual; pray/check/ order/count	Fluoxetine (40 mg, 3.5 mo; some)	GAD, obsessive-compulsive PD, anorexia nervosa (past), childhood motor tics (past)
5	40/M	7	Symmetry/ exactness; check/arrange	Fluvoxamine (300 mg, 8 mo; slight), fluoxetine (40–60 mg, 2.5 mo; none), paroxetine ("low dose," 4–5 mo; none)	Dysthymic disorder, substance abuse (past), obsessive-compulsive PD, tic-like mannerisms
6	33/M	8	Contamination/ exactness/sacrilege; repeat/check/ arrange/count	Clomipramine (150 mg, 1.5 y; improved), fluoxetine (20–30 mg, 6 mo; worse), bupropion[a] (none)	Substance abuse (past), GAD, paranoid PD, tic-like mannerisms, binge eating disorder,[b] depressive PD,[b] passive-aggressive PD[b]
7	36/F	27	Contamination/ exactness/ objects missing; decontaminate arrange/check	No past medication	None
8	47/F	Early childhood	Exactness/order; clean/arrange/ check	Fluvoxamine (not known, 2–3 wk; none), buspirone[a] (none), clonazepam[a] (none), bupropion[a] (none), lorazepam[a] (none)	GAD, social phobia, specific phobias, obsessive-compulsive PD

[a]Dose and duration not known.
[b]Disorder delineated for research purposes.
Abbreviations: 5-HTP = 5-hydroxytryptophan, GAD = generalized anxiety disorder, OCD = obsessive-compulsive disorder, PD = personality disorder, PTSD = posttraumatic stress disorder.

Repeated-measures analysis of variance (ANOVA) was used to determine the effect of duration of treatment on YBOCS ratings. Averages of ratings obtained off medication (obtained 1 week and 3–8 hours prior to treatment) and end-of-treatment ratings (obtained after 7 and 8 weeks of treatment) were used to determine the change in YBOCS score over the course of treatment for each subject. Our hypothesis was that ondansetron would be associated with a statistically significant reduction in mean YBOCS rating (paired t test, 1-tailed, $p < .05$) from baseline to end of treatment. "Significant improvement" was defined operationally as a decrease in YBOCS score of ≥ 35% between baseline and end of treatment. Statistics relating to ratings for depression and anxiety are also reported for informational purposes.

RESULTS

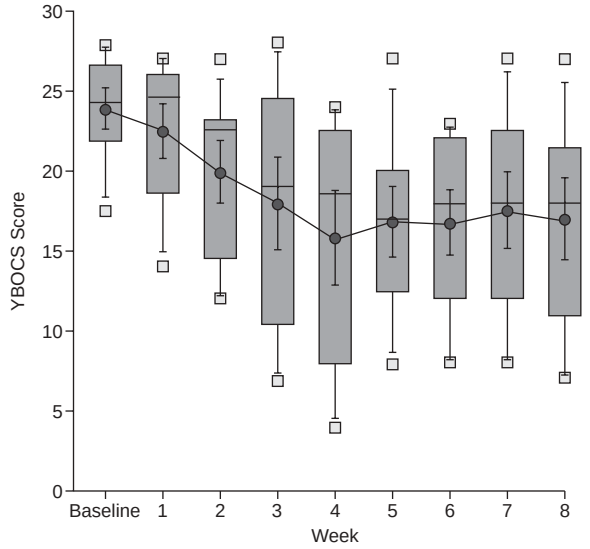
Repeated-measures ANOVA found a significant effect of treatment time on YBOCS scores ($p < .0001$) and on YBOCS Global Severity ratings ($p = .0011$) for the 8 subjects entering the study. Ondansetron treatment for these subjects was associated with a statistically significant reduction in YBOCS ratings ($p = .0054$) and YBOCS Global Severity scores ($p = .019$) from baseline to end of treatment. A statistically significant difference in YBOCS score was evident by the second week of treatment ($p = .0094$; Figure 1) . End-of-treatment YBOCS scores for the 8 subjects entering the study fell 28.5% from a mean baseline rating of 23.8 (Table 3). Mean global improvement as measured by the YBOCS GI item was 5.0,

Table 2. Treatment-Associated Somatic Symptoms

N	Symptom
5	Constipation
3	Dry mouth
2	No symptoms
2	Headache
1	Dry mouth
1	Worsening PMS-related mood variation
1	Flatulence, abdominal cramping, indigestion
1	Chest discomfort
1	Urinary urgency
1	Dizziness
1	Agitated depression
1	Bacterial cholecystitis

Abbreviation: PMS = premenstrual syndrome.

Figure 1. Distribution of Mean YBOCS Scores With Standard Error Bars Over 8 Weeks of Treatment (bold lines)[a]



[a]Superimposed are box plots indicating weekly medians and upper and lower quartile scores, with whiskers representing 95% confidence intervals for weekly medians and squares indicating extreme scores.
Abbreviation: YBOCS = Yale-Brown Obsessive Compulsive Scale.

representing a statistically significant improvement over the score 3.0 (no improvement; p = .0007). A score of 5 on this scale corresponds to "much improvement" in OCD symptoms.

Three subjects in the trial showed a reduction in YBOCS scores of greater than 35%, the criterion set for "significant improvement." Average symptom reduction for these subjects was 55%. For the 6 subjects completing the trial, mean YBOCS scores fell an average of 33%. Interestingly, for these 6 subjects who were available for follow-up 2 weeks after withdrawal from ondansetron, there was a statistically significant increase in YBOCS scores associated with discontinuing the medication (mean increase = 5.25; p = .0021), representing a 45% worsening of symptoms from end of treatment.

Table 3. Psychiatric Ratings Over the 8-Week Ondansetron Treatment Trial

	YBOCS				HAM-D		HAM-A	
Case No.	Base	End	% Change	YBOCS GI	Base	% Change	Base	% Change
1	23.0[a]	8.5	–63	6.0	8	–75	8	–88
2	17.5	16.5	–6	4.5	8	60	7	7
3	26.0	23.0	–12	5.0	3	–17	4	–63
4	20.5	7.5	–63	6.0	11	–55	20	–75
5	25.0	15.0	–40	5.5	7	–92	5	–47
6	23.5	19.0	–19	6.0	16	–10	20	–44
7	28.0	21.0[b]	–25[b]	4.0[b]	21	17[b]	14	56[b]
8	27.0	27.0[b]	0[b]	3.0[b]	18	–56[b]	12	–39[b]
Mean	23.8	17.2	–28.5	5.0	11.3	–28.3	11.4	–36.5

[a]Participant had only 1 baseline rating.
[b]Participant dropped out after week 6. Last rating carried forward.
Abbreviations: Base = average baseline scores, End = average scores for weeks 7 and 8, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = 21-item Hamilton Rating Scale for Depression, YBOCS = Yale-Brown Obsessive Compulsive Scale, YBOCS GI = average YBOCS Global Improvement rating from baseline rating for weeks 7 and 8 (3 = no change, 4 = minimally improved, 5 = much improved, 6 = very much improved).

Repeated-measures ANOVA also found statistically significant effects of treatment time on HAM-D scores (p = .0068) and HAM-A scores (p = .025). Although reductions in depression and anxiety between baseline and end-of-treatment ratings averaged 28% and 36%, respectively, the differences for these measures were not statistically significant because of high variance in end-of-study ratings attributable to an outlier (the patient in case 7 endured a severe psychosocial disturbance [abandonment] while on medication). Single-tailed analyses without this outlier revealed statistically significant reductions in both depression (p = .046) and anxiety (p = .011) in association with ondansetron treatment.

In the past, it has been useful to consider whether subgroups of OCD patients were more or less likely to respond to novel treatments. In this study, the presence of tic-like mannerisms appeared to be a positive prognostic factor in treatment outcome. All 3 individuals having such mannerisms were "much improved" or "very much improved" at the end of the trial, averaging a reduction in YBOCS score of 41%. A fourth subject without such mannerisms, but with a history of childhood motor tics, also experienced a significant improvement (40%) in symptoms. In contrast, the 4 subjects without tic-related symptoms averaged an 11% improvement in their YBOCS scores. This observation is consistent with a report that ondansetron reduced OCD symptoms in 2 of 3 Tourette disorder patients with comorbid OCD[36] and might suggest that 5-HT_3 antagonism could have some benefit in treating tic-associated OCD symptoms.

There was no clear-cut relationship between previous SRI response history and improvement associated with ondansetron treatment. One subject who experienced "some" improvement on her only SRI trial had a 63% reduction in her YBOCS score while taking ondansetron.

Of the 2 subjects who had failed 2 SRI trials lasting over 10 weeks at adequate doses, 1 improved significantly on ondansetron treatment (40%) while the other did not (6%). The 2 subjects who had failed one SRI trial but had shown "some" or "definite" improvement on a second trial averaged an 18% reduction in YBOCS scores.

DISCUSSION

In this small pilot trial, ondansetron treatment for 8 weeks was associated with a statistically significant reduction in YBOCS rating scores, representing an average reduction of over 28%. The reduction was rapid in onset, becoming significant in the second week of treatment. This reduction is on the low side relative to average responses seen in the multicenter trials of SRIs in OCD (23%–43%).[10] On average, subjects were "much improved" by YBOCS GI measurement. Thirty-eight percent of subjects experienced a "clinically significant" drop in YBOCS ratings during the trial. This response rate is slightly less than those reported for SRIs (43%–60%).[10]

There are several caveats in considering the results of this pilot trial. This was an open-label, uncontrolled trial. One must recognize that increased attention to OCD symptoms and positive expectations may have contributed to the improvement seen with this treatment. One must also consider the small sample size and limited duration of medication treatment (8 weeks). OCD symptoms in patients treated with SRIs in placebo-controlled trials continue to improve for up to 12 weeks and beyond.[11] It is not known whether the improvement seen in this study would continue or be sustained in a longer trial. As a further caveat, it should also be noted that constipation was associated with ondansetron treatment in 5 of the 8 subjects in the study. While this did not limit participation in this study, it is a factor that should be considered in any clinical decision to use ondansetron for treatment of OCD.

There are also factors that may have limited our ability to appreciate the potential of 5-HT_3 antagonist treatment in OCD. The daily dose of ondansetron in this trial was approximately 15% of the minimum dose recommended for nausea and emesis.[41] Ondansetron has a relatively short serum half-life (5.7 hours),[41] and serum concentrations (not measured) may have fallen to as low as 25% of maximum levels during overnight intervals. Ondansetron also has low permeability across the blood-brain barrier.[42] As such, it is conceivable that the dose of ondansetron in this trial may have been insufficient to achieve maximal benefit. Also, rating anomalies may have partially obscured potential benefits of ondansetron treatment. One nonresponder by our YBOCS criteria experienced a 7-hour/day (47%) reduction in time occupied by his obsessions; however, this improvement did not change the obsession/time item score on his YBOCS rating. A comparable discrepancy occurred in rating the time occupied by his compulsions. Two other subjects reporting minimal responses while on medication indicated that their OCD had actually improved significantly in retrospect, when faced with a resurgence of their symptoms after coming off the medication. A larger placebo-controlled double-blind trial should reduce the impact of both positive expectation biases and rating anomalies in assessing the benefits of ondansetron treatment in OCD.

Currently there are few available psychotropic medications that are 5-HT_3 receptor antagonists. Of those available, the antidepressant mirtazapine has the highest affinity for 5-HT_3 sites[43] (approximately 3 times weaker than ondansetron).[44] In a recent pilot trial, mirtazapine treatment was associated with significant improvement in OCD symptoms in 2 of 6 subjects completing the trial.[45] Given our findings, it is conceivable that 5-HT_3 receptor antagonism may have contributed to this improvement. Such findings raise the possibility that mirtazapine might also potentially be useful as an adjunct to SRI treatment of OCD. In this vein, one might note that atypical neuroleptics have been used successfully to augment the action of SRIs in treatment-refractory OCD.[46] Certain atypicals, such as olanzapine and clozapine, have weak affinity for 5-HT_3 receptors[47] (approximately 40–45 times weaker than ondansetron[44]); however, others such as risperidone have virtually no affinity for these sites.[48] Because atypicals without 5-HT_3 activity are effective adjuncts in OCD treatment,[46] it is unlikely that 5-HT_3 antagonism is the primary mechanism by which atypical neuroleptics exert their antiobsessive effects.

Finally, it is paradoxical that SRIs would have antiobsessive effects when they presumably would activate 5-HT_3 receptors in association with increased synaptic serotonin concentrations. In theory, such activation should be anxiogenic, acting against the antiobsessive effects of SRIs. Indeed, an initial increase in the severity of OCD symptoms has been noted in association with SRI treatment.[49] Concurrent treatment with a 5-HT_3 antagonist could potentially reduce this problematic effect and augment the ultimate efficacy of SRIs by reducing the putative risk-aversive effects of 5-HT_3 stimulation. Additionally, 5-HT_3 antagonism could potentially be effective as an adjunct in behavior therapy. As indicated, approximately 30% of OCD patients are unwilling to engage in behavior therapy because of fears relating to their obsessions.[3] Such reluctance can limit effectiveness and retard progress in behavioral therapy. By reducing exaggerated perceptions of risk, 5-HT_3 antagonists might well increase a patient's willingness to engage in exposure therapy. For these reasons, pilot trials employing 5-HT_3 antagonists as adjuncts for both SRI and behavioral therapies may be warranted.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa), clomipramine (Anafranil and others), clonazepam (Klonopin and others), clozapine (Clozaril and others), desipramine (Norpramin and others), diazepam (Valium, Diastat, and

others), fluoxetine (Prozac and others), lorazepam (Ativan and others), mirtazapine (Remeron), nefazodone (Serzone), olanzapine (Zyprexa), ondansetron (Zofran), paroxetine (Paxil), risperidone (Risperdal), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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