Serotonin-1D Hypothesis of Obsessive-Compulsive Disorder: An Update

Joseph Zohar, M.D.; James L. Kennedy, M.D.;
Eric Hollander, M.D.; and Lorrin M. Koran, M.D.

Support for the serotonin-1D (5-HT_{1D}) hypothesis of obsessive-compulsive disorder (OCD) and related conditions comes from a variety of sources. Some pharmacologic challenges with the 5-HT_{1D} agonist sumatriptan, and case reports in which prolonged administration of 5-HT_{1D} agonists was associated with a therapeutic effect, suggest that 5-HT_{1D} may play a role in obsessive-compulsive symptoms. Genetic studies have also found that polymorphism of the 5-HT_{1D} gene may be preferentially transmitted to those patients with OCD. However, taking into account that OCD is a heterogeneous syndrome, the 5-HT_{1D} hypothesis requires further investigation in order to disentangle the role of the 5-HT_{1D} receptor in this common and often severe disorder. *(J Clin Psychiatry 2004;65[suppl 14]:18–21)*

The pathophysiology of most mental disorders has yet to be elucidated. One way to study pathophysiology is by specific activation of the system or receptor(s) hypothesized to be relevant, i.e., pharmacologic challenge. A pharmacologic challenge is designed to induce a set of specific and relevant symptoms (e.g., exacerbation of obsessions and compulsions in the case of obsessive-compulsive disorder [OCD]). These challenges can implicate a specific neurotransmitter receptor or system. In addition, the pharmacologic actions of medications that have a beneficial effect in a disorder or in related disorders can also point toward the disorder's biological cause. In OCD, both sources of evidence point to the serotonin (5-HT) neurotransmitter system.

Some researchers have conducted pharmacologic challenges utilizing serotonin agents in patients with OCD to determine the role of 5-HT in the pathogenesis of OCD. For example, *meta*-chlorophenylpiperazine (*m*-CPP) was found to exacerbate OCD symptoms in 4 studies[1–4] but not in 2 others.[5,6] Other anxiogenic challenges, however, have not provoked the same response. The lack of specific symptom changes following administration of lactate,[7] carbon dioxide,[8] yohimbine,[9] and cholecystokinin receptor agonists[10] suggests that OCD patients are not sensitive to all anxiogenic challenges and that the serotonergic component of the *m*-CPP challenge may play a critical role in the pathology of OCD.

The strongest and most consistent evidence for the involvement of the serotonin system in OCD is that, to date, only serotonergic antidepressant medications are effective treatments for the disorder. This specific response is well documented in studies in which serotonergic antidepressants but not comparator noradrenergic antidepressants were found to be effective.[1,6] In one study,[1] the serotonergic tricyclic antidepressant (TCA) clomipramine was found to be effective, but the noradrenergic TCA desipramine was not. In another study,[6] the selective serotonin reuptake inhibitor (SSRI) fluvoxamine, but not the noradrenergic antidepressant desipramine, was an effective treatment for OCD. Although these studies suggest that 5-HT may be involved in the therapeutic effects, they do not necessarily indicate that 5-HT is related to the pathophysiologic basis of this disorder. Moreover, there are multiple serotonin receptors, and serotonin modulates a variety of central nervous system pathways and functions. Hence, further work is needed to determine which (if any) of the serotonin receptors is involved in OCD.

DETERMINING WHICH SEROTONIN RECEPTORS ARE INVOLVED IN OCD AND RELATED DISORDERS

One method to determine which serotonin receptors are involved in OCD and related disorders is to compare the receptor profile of serotonergic agents that exacerbate obsessive-compulsive symptoms with those serotonergic agents that do not (Table 1).

From the Division of Psychiatry, Chaim Sheba Medical Center, Tel Hashomer, Tel Aviv University, Israel (Dr. Zohar); the Centre for Addiction and Mental Health, University of Toronto, Ontario, Canada (Dr. Kennedy); the Department of Psychiatry, Mount Sinai School of Medicine, New York, N.Y. (Dr. Hollander); and the Department of Psychiatry and Behavioral Sciences, Stanford University Medical Center, Calif. (Dr. Koran).

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Corresponding author and reprints: Joseph Zohar, M.D., Division of Psychiatry, Chaim Sheba Medical Center, Tel Hashomer, 52621 Israel (e-mail: jzohar@post.tau.ac.il).

Table 1. The Effects of Different Agents on OCD Symptoms and Serotonin Receptors

Agent	OCD Effect	Effect on Serotonin Receptor				
		5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2C}$	5-HT$_3$
m-CPP (oral)[1–4]	Worse	Agonist	…	Agonist	Partial agonist	Agonist
MK-212[11]	None	Agonist	Agonist	None	Agonist	…
Ipsapirone[12]	None	Agonist	…	None	…	…
Sumatriptan[13–15]	Worse	…	…	Agonist	…	…
Metergoline[2]	None	Antagonist	Antagonist	Antagonist	Antagonist	…

Abbreviations: 5-HT = serotonin, *m*-CPP = *meta*-chlorophenylpiperazine, OCD = obsessive-compulsive disorder.

m-CPP exacerbates OCD symptoms according to some,[1–4] although not all,[5,6] studies. In one of these studies,[2] some subjects with OCD were given metergoline, a nonselective serotonin antagonist, prior to receiving *m*-CPP. Other subjects received placebo, *m*-CPP only, or metergoline only. Subjects who received *m*-CPP only experienced an increase in anxiety and obsessive-compulsive symptoms, but those who received metergoline first did not. Since preadministration of metergoline blocked the exacerbation, the authors concluded that the exacerbation of obsessive-compulsive symptoms was indeed related to the 5-HT system.

Because *m*-CPP affects several serotonin receptors, its effects do not specify which receptor is most involved. MK-212 is also a serotonin agonist, but it has no effect on the intensity of OCD symptoms, although it does affect anxiety symptoms.[11] MK-212 does not affect all of the serotonin receptors affected by *m*-CPP. When ipsapirone, a 5-HT$_{1A}$ agonist, was given to OCD patients and healthy controls to determine its impact on OCD symptoms,[12] no such effect was found. Of these 3 agents—*m*-CPP, MK-212, and ipsapirone—the only one that exacerbates OCD symptoms is also the only one with activity at the 5-HT$_{1D}$ receptor, suggesting that the 5-HT$_{1D}$ receptor may be involved in the pathophysiology of OCD.

The 5-HT$_{1D}$ receptor has one role as a presynaptic autoreceptor that under normal conditions reduces serotonin transmission. Theoretically, in the brain of a person with OCD, this receptor could be hypersensitive. This theory would explain why a 5-HT$_{1D}$ agonist like *m*-CPP can cause acute worsening of OCD symptoms. Moreover, 5-HT$_{1D}$ is densely located in the basal caudate area as well as prefrontal areas, regions that are part of the brain circuitry involved in OCD. The 5-HT$_{1D}$ receptor also has a second role in postsynaptic locations. The presynaptic and postsynaptic presence of the 5-HT$_{1D}$ receptor raises the possibility that it modulates and regulates obsessive-compulsive behaviors.

To further explore the possibility that 5-HT$_{1D}$ is involved in OCD, Stern et al.[13] and Gross-Isseroff et al.[14] conducted a challenge study with the 5-HT$_{1D}$ agonist sumatriptan. They hypothesized that if 5-HT$_{1D}$ is indeed involved in OCD, then activation of this receptor by sumatriptan, which is usually used to treat migraine headaches, would be associated with a worsening of obsessive-compulsive symptoms. Indeed, transient exacerbation of OCD symptoms, comparable to the exacerbation observed after administration of *m*-CPP, was observed.

These results were partially replicated by Koran and colleagues,[15] who studied 10 medication-free OCD patients. For 5 days, 5 patients received 100 mg/day of sumatriptan, and 5 patients received placebo. Obsessive-compulsive symptoms worsened in the 5 sumatriptan-treated patients, whereas symptoms improved slightly in the placebo-treated patients. This difference in symptom severity as measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS) was statistically significant ($p < .015$) for sumatriptan-treated patients versus placebo-treated patients.

Another study,[16] however, found that sumatriptan did not acutely exacerbate obsessive-compulsive symptoms. After a drug washout period, 15 patients received sumatriptan, 100 mg/day, on one occasion and placebo 1 week later. Although mean YBOCS scores increased from baseline under both challenge conditions, the change was not significant. The investigators concluded that sumatriptan may not be the best agent to determine the role of 5-HT$_{1D}$ receptors in OCD, since it does not penetrate the blood-brain barrier as effectively as do other 5-HT$_{1D}$ agonists such as zolmitriptan. However, a subsequent study[17] of a zolmitriptan challenge in 16 patients with OCD noted no change in obsessive-compulsive symptoms. The difference in results between longer-term administration of sumatriptan, e.g., the 5-day sumatriptan treatment of Koran et al.[15] and the 4- to 5-week treatment by Stern et al.[13] (described below), and single-dose challenge studies indicates a need for caution in interpreting 5-HT$_{1D}$ challenge studies. Since acute neuronal response to a single serotonergic challenge and long-term neuronal and neuronal pathway responses to continuous challenge are undoubtedly different, we cannot draw firm conclusions about the possible role of the 5-HT$_{1D}$ receptor in OCD pathophysiology from the results of acute challenges alone.

Functional brain imaging has also demonstrated that sumatriptan can be associated with worsening of obsessive-compulsive symptoms. Stein et al.[18] conducted a double-blind, placebo-controlled, randomized study of sumatriptan, 100 mg/day, in 14 patients with DSM-IV OCD. Ninety minutes after drug administration, patients underwent single-photon emission computed tomography of the brain. Patients were then started on treatment with an SSRI. The patients who experienced acute symptom exacerbation exhibited decreased activity in frontal areas of the brain and poorer response to SSRI treatment than those patients who did not. The investigators hypothesized that in some patients hyperactivity in frontal areas may be a compensatory mechanism for coping with OCD, instead of

Table 2. Genes and Gene Products Possibly Implicated in Obsessive-Compulsive Disorder[a]

5-HT_{1D}
5-HT_{2A}
5-HTT/*SLC6A4*
COMT
DRD4
MAO-A
MOG-4

[a]Based on Pato et al.[23]
Abbreviations: 5-HT = serotonin, 5-HTT = serotonin transporter, COMT = catechol *O*-methyltransferase, DRD4 = dopamine D_4 receptor, MAO-A = monoamine oxidase A, MOG = myelin oligodendrocyte glycoprotein.

a cause of OCD. This explanation would be consistent with their finding that decreased frontal activity was associated with symptom exacerbation. These results provide further support for the potential role of 5-HT_{1D} in OCD pathophysiology.

Hollander et al.[19] extended the relevance of 5-HT_{1D} beyond OCD to repetitive behavior across neuropsychiatric disorders. In this study, the investigators reported that the growth hormone response to administration of sumatriptan in adult autistic patients was significantly positively correlated with the severity of compulsive symptoms measured by the YBOCS compulsion score. Higher growth hormone response was correlated with greater severity of compulsion. In contrast, 5-HT_{1D} sensitivity was not correlated with the severity of autism or the other symptom domains of social or language function, but only to the repetitive behavior domain.

USING THE 5-HT_{1D} HYPOTHESIS TO IDENTIFY EFFECTIVE TREATMENT FOR OCD AND RELATED DISORDERS

The efficacy of the SSRIs in OCD is well established. If 5-HT_{1D} pathology is related to OCD, that could partially explain why patients with OCD tend to require higher doses of SSRIs than patients with depression or other anxiety disorders and why it takes longer for them to respond; the 5-HT_{1D} receptor appears to be a somewhat "sticky" receptor that requires a longer time and higher dose for desensitization.[20]

SSRIs, by increasing the synaptic availability of serotonin, affect all serotonin receptors; some of these receptors, of course, may not be involved in OCD pathophysiology. Theoretically, if OCD is associated with an excessive behavioral hypersensitivity, then chronic administration of an agonist for the relevant receptor(s) will be associated with therapeutic response. This result was noted by Stern et al.,[13] who reported acute reductions in both depressive and obsessive-compulsive symptoms in 3 treatment-resistant OCD patients who received 100 mg of sumatriptan orally for 4 to 5 weeks as an augmentation therapy. A case report also supports a potential therapeutic use for 5-HT_{1D} agonists like sumatriptan in OCD.[21] The authors describe a 15-year-old boy who presented with contamination obsessions and compulsive washing rituals, for which he had been unsuccessfully treated with a number of SSRIs, clomipramine, and risperidone. After 4 weeks of treatment with sumatriptan, the patient's Children's YBOCS score dropped from 29 to 23. At that point, sumatriptan treatment was stopped and fluoxetine treatment was begun. After 6 months of fluoxetine treatment, this patient's Children's YBOCS score was 3. He was eventually able to stop treatment altogether, with no symptom recurrence. Given that treatment was open-label in both the case series of Stern et al.[13] and in this case report, a placebo response cannot be ruled out.

More clinical studies are needed to determine whether 5-HT_{1D} agonists acutely exacerbate OCD symptoms as well as whether these agents may be effective treatments for the disorder.

USING GENETIC FINDINGS TO CONFIRM THE 5-HT_{1D} HYPOTHESIS AND IDENTIFY POSSIBLE TREATMENTS

Family and genetic studies may provide support for a discrete pathophysiology, provided that it is genetically based. Family studies have shown a higher rate of OCD among relatives of patients with OCD than among relatives of healthy controls. This finding may imply a degree of genetic heritability in certain subtypes of OCD, but, because of the study designs, a learned behavior component cannot be ruled out. For example, Pauls and colleagues[22] interviewed 466 first-degree relatives of 100 probands with OCD and 113 first-degree relatives of psychiatrically healthy control subjects. The investigators found that OCD, subthreshold OCD, and tics were significantly ($p < .05$) more common in relatives of OCD probands than in relatives of control subjects.

A number of candidate genes possibly involved in OCD and related disorders have been identified, among them the 5-HT_{1D} gene (Table 2). The *G* and *C* alleles of this gene differ by a single base pair. This difference changes the amino acid coded and has some functional implications. Mundo and colleagues[24] have studied the association between OCD and the *G* allele of the G861C polymorphism of the 5-HT_{1D} gene as well as the linkage disequilibrium between this polymorphism and the T371G polymorphism in patients with OCD and their families (N = 121 families). The *G861* allele was preferentially transmitted to those patients with OCD symptoms ($p = .02$). Another study[25] reported higher YBOCS obsession scores in those subjects with preferential transmission of the *G861* allele versus those with the *C861* allele. These results suggest that the *G* allele of the 5-HT_{1D} gene plays a role in at least some aspects of OCD symptomatology. This finding was replicated in a study[26] in which G861C polymorphism of

the $5HT_{1D}$ gene was analyzed in a sample of 72 trios, but not in another study.[27] Once the genetics of OCD are understood, different interventions for specific phenotypes of the disorder can be developed.

CONCLUSION

Support for the 5-HT_{1D} hypothesis of OCD currently derives from pharmacologic challenges that demonstrate exacerbation of obsessive-compulsive symptoms following activation of 5-HT_{1D} receptors, from clinical reports that suggest a potential therapeutic utility of prolonged oral administration of 100 mg/day of sumatriptan, and from genetic studies that suggest a role for polymorphism of the 5-HT_{1D} gene in OCD. Studies utilizing triptans that more readily pass the blood-brain barrier, such as naratriptan, rizatriptan, and zolmitriptan are warranted.[28] Further work focusing on the possible interaction between 5-HT_{1D} polymorphism, utilizing functional brain imaging in parallel with phenotyping, and measuring responses to specific interventions is warranted in order to further explore the role of 5-HT_{1D} in the obsessive-compulsive spectrum in general and in OCD in particular. In addition, genetic studies should explore the links between 5-HT_{1D} alleles and possible markers of different pathophysiologic types of OCD (e.g., different OCD symptom types, age at onset, presence/absence of comorbid mood or impulse-control disorders, and speed or degree of therapeutic response to SSRIs). Finally, investigations of the effect on behavior of deleting the 5-HT_{1D} receptor in knockout mice or in a knockout mouse strain that exhibits compulsive behaviors, such as the 5-HT_{2C} receptor knockout mouse,[29] may be informative.

Drug names: clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), naratriptan (Amerge), risperidone (Risperdal), rizatriptan (Maxalt), sumatriptan (Imitrex), zolmitriptan (Zomig).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, risperidone and sumatriptan are not approved by the U.S. Food and Drug Administration for treatment-resistant OCD; and zolmitriptan, metergoline, and ipsapirone are not approved as a pharmacologic challenge for OCD.

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