Open Trial of Flutamide for Treatment of Obsessive-Compulsive Disorder

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Background: Several lines of evidence suggest that gonadal steroid hormones play a role in the onset and exacerbation of obsessive-compulsive disorder (OCD). In this study, we examined the effects of treatment with flutamide, a synthetic, nonsteroidal, competitive antagonist of the androgen receptor, on OCD symptoms.

Method: Eight outpatients meeting DSM-III-R criteria for OCD participated in an 8-week open trial of flutamide. The dose was increased from 250 mg/day to 750 mg/day over the first 4 weeks and maintained at 750 mg/day for the final 4 weeks. The primary outcome measures for OCD symptoms were the Yale-Brown Obsessive Compulsive Scale and the Maudsley Inventory and for anxiety symptoms, the Beck Anxiety Inventory and the Hamilton Rating Scale for Anxiety. Subjects also provided self-ratings of aggression and sexual interest and activity.

Results: There were no reductions in measures of obsession and compulsions or measures of anxiety over the 8-week trial. However, self-ratings of feelings of aggression did fall significantly over the 8-week trial ($p < .001$).

Conclusion: The lack of response to treatment with flutamide, an androgen receptor antagonist, suggests that any effects of gonadal steroids to exacerbate OCD symptoms are more likely to be mediated through estrogen receptors or through mechanisms that do not involve classical intracellular androgen receptors. Future treatment trials should examine agents that antagonize estrogen receptors or otherwise inhibit estrogen activity.

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Obsessive-compulsive disorder (OCD) is an anxiety disorder characterized by intrusive, recurrent thoughts and ritualized, repetitive behaviors that are experienced as irrational or excessive. Although serotonin reuptake inhibitors are the current standard pharmacologic treatment for OCD, most patients have only a partial response to these agents, and 25% of patients have no response.[1] Low-dose neuroleptics have been shown to be an effective augmentation agent for a subgroup of OCD patients treated with serotonin reuptake inhibitors,[2] but no other psychopharmacologic treatments have proved to be beneficial in controlled trials.[3–7]

Several lines of evidence suggest that modulation of gonadal steroid systems may be a useful alternative treatment approach. Two published case series and 2 case reports have described a reduction in OCD symptoms during treatment with drugs that antagonize gonadal steroids.[8–12] Casas et al.[8] conducted an open study with cyproterone acetate, an androgen synthesis inhibitor and androgen receptor antagonist that also suppresses luteinizing hormone release, in 5 patients with severe obsessive-compulsive symptomatology. These patients experienced a marked improvement with a gradual reemergence of obsessive-compulsive symptoms after 3 to 6 months of treatment. Leonard[9] reported 2 childhood cases of OCD that were successfully treated with a combination of spironolactone, an androgen receptor antagonist, and testolactone, an aromatase inhibitor. An 8-year-old boy experienced remission that lasted for 6 months, and a 15-year-old boy had a moderate improvement throughout a 10-week trial. More recently, Weiss et al.[11] described another case of OCD improvement in response to cyproterone acetate treatment, and Chouinard et al.[12] reported beneficial effects of aminoglutethimide, a drug that globally inhibits steroid biosynthesis, in a treatment-resistant OCD patient.

In addition, several conditions characterized by increased gonadal steroid production have been associated with the onset and exacerbation of OCD symptoms. These conditions include pregnancy,[13,14] polycystic ovary disease,[11] and the luteal phase of the menstrual cycle.[15]

Unfortunately, the gonadal steroid treatment regimens used in OCD patients in these studies and the reproductive events associated with symptom exacerbation have

Table 1. Clinical Characteristics of Study Subjects

Patient	Sex	Age (y)	Age at Onset (y)	Other Diagnoses	Menstrual Status	Treatment Response to SSRI (1–5)[a]	Primary Symptoms	Symptom Severity (1–5)[a]	Tics
1	F	34	12	Anorexia nervosa	Amenorrheic	2	Symmetry	3	No
2	F	58	26	None	Postmenopausal	3	Contamination	3	No
3	M	38	15	Dysthymia, social phobia, alcohol abuse		1	Checking, aggressive thoughts	2	Yes
4	M	36	8	Major depression		1	Checking, contamination	4	No
5	M	45	13	Dysthymia		3	Checking	3	Yes
6[b]	F	37	20	Dysthymia	Regular	4	Contamination	3	No
7	M	23	8	Panic		5	Checking, aggressive thoughts	3	Yes
8	M	28	20	None		1	Checking, repeating	4	Yes

[a]Prior or later response to selective serotonin reuptake inhibitor (SSRI) and symptom severity were scored from 1–5, with 1 being the lowest and 5 being the highest.
[b]Patient with 35% improvement in obsessive-compulsive disorder symptom ratings.

relatively nonspecific and complex effects on gonadal steroid systems. This has made it difficult to identify which particular steroids or steroid receptors are most important in mediating the effects of gonadal steroids on OCD.

To determine whether gonadal steroids exacerbate OCD by activating androgen receptors, we administered an 8-week open trial of flutamide to 8 patients with chronic OCD. Flutamide is a synthetic, nonsteroidal, competitive antagonist of the androgen receptor[16] that has been used for treatment of prostate cancer,[17] prostatic hypertrophy,[18] and hirsutism.[19] Flutamide has no intrinsic hormonal or antihormonal activity other than its ability to block androgen action at the androgen receptor.[20] We expected that flutamide treatment would reduce the severity of OCD symptoms.

METHOD

Subjects were 8 white outpatients (3 women and 5 men) meeting DSM-III-R criteria for OCD.[21] Patients were diagnosed by the Structured Clinical Interview for DSM-III-R (SCID)[22] administered by a psychologist and a clinical interview with a psychiatrist. Subjects had been off all medications, including estrogen replacement, for at least 8 weeks prior to entering the study. Clinical characteristics of the subjects are listed in Table 1.

Flutamide was administered orally in a single 250-mg dose for the first 2 weeks, 2 divided 250-mg doses (500 mg/day) for the second 2 weeks, and 3 divided 250-mg doses (750 mg/day) for the remaining 4 weeks of the 8-week trial.

The following measures were used every 2 weeks to monitor changes in psychological symptoms. Observer-rated scales included (1) the Yale-Brown Obsessive Compulsive Scale (Y-BOCS),[23] (2) the Hamilton Rating Scale for Depression (HAM-D),[24] and (3) the Hamilton Rating Scale for Anxiety (HAM-A).[25] Self-rated scales included (1) the Profile of Mood States (POMS),[26] (2) the University of Miami Modified Maudsley Obsessive Compulsive Inventory,[27] and (3) the Beck Anxiety Inventory.[28] In addition to these standardized measures, we included 7-point Likert scales that assessed irritability, feelings of aggressiveness, and sexual interest and activity.

The study was approved by the National Institute of Mental Health Institutional Review Board, and all subjects gave written informed consent to participate.

The effect of flutamide treatment on symptom measures was analyzed using repeated-measures analysis of variance.

RESULTS

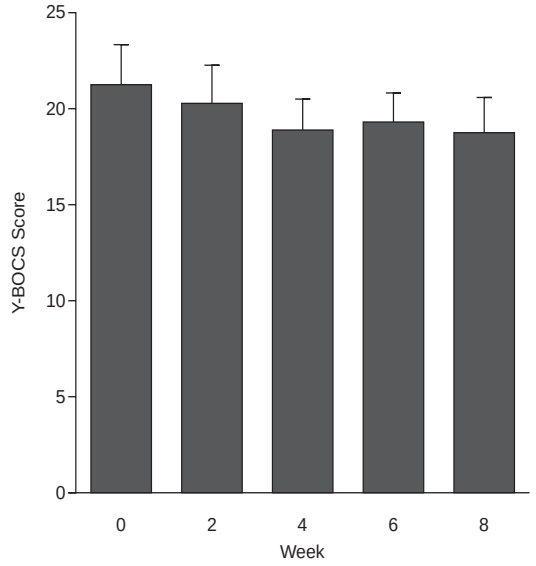
Subjects as a group demonstrated no significant improvement in OCD symptoms as rated by the Y-BOCS ($F = 1.39$, $df = 4,28$; $p = .26$) (Figure 1) or the Maudsley Inventory ($F = 0.57$, $df = 4,24$; $p = .68$). Subjects also reported no significant reductions in anxiety as measured by the Beck Anxiety Inventory ($F = 0.52$, $df = 4,28$; $p = .72$) or the HAM-A ($F = 0.68$, $df = 4,28$; $p = .62$). Depressive symptoms remained unchanged as rated by the HAM-D ($F = 1.05$, $df = 4,28$; $p = .40$). There was also no significant change in any of the POMS subscales (tension-anxiety, depression-dejection, anger-hostility, vigor, fatigue, confusion) or the POMS total mood disorder score.

Subjects did report feeling significantly less aggressive on the Likert scale ($F = 6.37$, $df = 4,28$; $p < .001$) as the trial progressed (Figure 2). There were no significant changes in irritability, libido, or sexual activity.

DISCUSSION

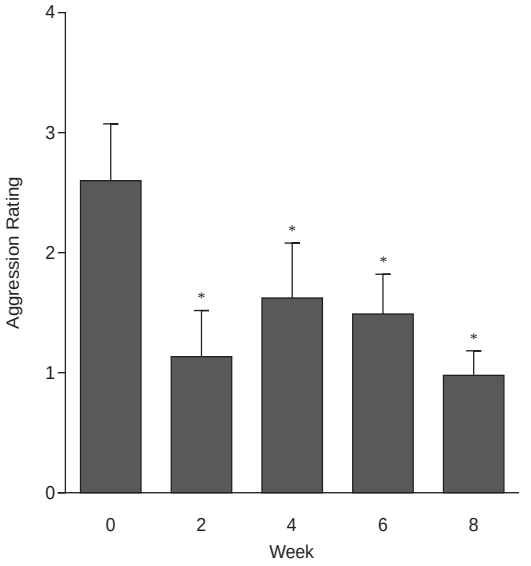
Eight weeks of flutamide treatment, with the final 4 weeks at a dosage known to effectively antagonize androgen receptors, had no significant effect on severity of OCD or anxiety symptoms in these 8 OCD patients. Examination of the responses of individual patients showed that 1 woman did experience a 35% reduction in OCD symptoms during the flutamide trial. These results con-

Figure 1. No Change in Y-BOCS Score During Flutamide Treatment[a]



[a]Abbreviation: Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Figure 2. Significant Reduction in Aggressive Feelings Self-Rating Scores During Flutamide Treatment



*p < .001.

trast with a report by Peterson et al.[29] of a beneficial effect of flutamide on tics in 3 of 3 patients with Tourette's disorder and a 38% improvement in OCD symptom severity in the only 1 of these 3 patients who had comorbid OCD.

The lack of response to treatment with an androgen receptor antagonist in OCD suggests that any effects of gonadal steroids that exacerbate OCD symptoms are more likely to be mediated through estrogen receptors or receptor-independent mechanisms. Testosterone is converted to estrogen by aromatization in many tissues, including the brain. Modulation of OCD symptoms through estrogen receptor systems would be compatible with evidence of exacerbation of OCD symptoms by gonadal steroids in patients of both sexes. Progesterone could also play a role in exacerbation of OCD in women, but levels in men are uniformly low. The drop in self-ratings of aggression during flutamide treatment suggests that in contrast to obsessions and compulsions, feelings of aggressiveness are, at least in part, mediated by androgen receptors.

Estrogen may modulate OCD symptom expression through several potential mechanisms. First, estrogen is known to modulate central serotonergic activity. Reported effects of estrogen treatment on serotonergic systems include increased tryptophan hydroxylase mRNA expression in the dorsal raphe,[30] increased serotonin (5-HT) transporter mRNA expression in the dorsal raphe,[31] increased density of serotonin transporter binding in multiple other brain areas,[31,32] and increased density of 5-HT_{2A} receptor binding in the dorsal raphe and several cortical and limbic areas.[33] Second, estradiol potentiates dopamine activity in the striatum[34] and has region-specific effects on striatal dopamine D_2 receptor binding.[35] Third, preclinical studies indicate that gonadal steroids act through estrogen receptors to enhance expression of the neuropeptide vasopressin in limbic areas, including the amygdala and the bed nucleus of the stria terminalis.[36,37] Vasopressin has been reported to be elevated in the cerebrospinal fluid of OCD patients,[38] and cerebrospinal fluid levels seem to be reduced by treatment with serotonin reuptake inhibitors, both in patients with OCD[39] and patients with depression.[40] There is also preclinical evidence that serotonin reuptake inhibitors are distinguished from other antidepressant agents by reducing hypothalamic vasopressin release.[41] Finally, estrogens can inhibit activity of the enzyme catechol-*O*-methyltransferase, and the low activity allele of this enzyme has been identified as a genetic risk factor for OCD.[42]

In summary, flutamide does not appear to be an effective treatment for obsessive-compulsive disorder. Further attempts to explore potential beneficial effects of gonadal steroid antagonism on OCD symptomatology should consider treatment regimens that antagonize estrogen receptors or otherwise inhibit estrogen activity.

Drug names: aminoglutethimide (Cytadren), flutamide (Eulexin), spironolactone (Aldactazide), testolactone (Teslac).

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