Double-Blind, Placebo-Controlled Trial of Topiramate Augmentation in Treatment-Resistant Obsessive-Compulsive Disorder

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Background: From 40% to 60% of obsessive-compulsive disorder (OCD) patients fail to tolerate or respond to selective serotonin reuptake inhibitors (SSRIs). Preclinical and neuroimaging studies have shown abnormally high glutamatergic concentrations in OCD patients and an association between decreased caudate glutamatergic concentrations and reduced OCD symptom severity after SSRI treatment. Topiramate inhibits glutamatergic conduction.

Method: Thirty-six adult patients with *DSM-IV*–defined OCD were randomly assigned to topiramate (n = 18) and placebo (n = 18) groups in this 12-week, double-blind, placebo-controlled, parallel-groups trial. Subjects were taking the maximum SSRI dose they could tolerate for at least 12 weeks and their current dose for at least 6 weeks, which was maintained throughout the study. Primary outcome measures were changes in the Yale-Brown Obsessive Compulsive Scale (YBOCS) total score and compulsions and obsessions subscores. Patients were recruited and followed up between April 1, 2003, and April 13, 2006.

Results: Using mixed regression models (time [weeks] × treatment), we found a significant treatment effect on the YBOCS compulsions ($P = .014$) subscale, but not the obsessions ($P = .99$) subscale or the total score ($P = .11$). Over the 12-week trial, the topiramate group (mean endpoint dose = 177.8 ± 134.2 mg/d; range, 50–400 mg/d) showed an average linear decrease of 5.38 points on the compulsions subscale compared to 0.6 points in the placebo group. Thirteen topiramate and 14 placebo subjects completed the study. Topiramate was not well tolerated in this trial: 28% (5/18) of the subjects discontinued the drug for adverse effects, and 39% (7/18) had a dose reduction for this reason.

Conclusions: The results of this first double-blind, placebo-controlled trial of topiramate augmentation for treatment-resistant OCD suggest that topiramate may be beneficial for compulsions, but not obsessions. Modifications in glutamatergic function may be responsible, at least in part, for the improved response in compulsions seen with topiramate.

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Obsessive-compulsive disorder (OCD) is a relatively common, chronic illness associated with considerable morbidity and economic and social burden.[1–6] Several neurotransmitter systems have been implicated in the pathophysiology of OCD. The many studies demonstrating the efficacy of selective serotonin reuptake inhibitors (SSRIs) in treating OCD support a role for serotonin in this disorder. Studies investigating serotonin receptor function support its pivotal role, and OCD symptoms are exacerbated following acute administration of meta-chlorophenylpiperazine, a serotonin 5-HT_{2C} and 5-HT_{1D} agonist,[7,8] and of sumatriptan, a 5-HT_{1D} agonist.[9] Recently, Adams et al[10] found increased 5-HT_{2A} receptor binding in the caudate nuclei of untreated OCD patients. One possible explanation for the seeming paradox of the efficacy of SSRIs in OCD, but the greater severity of OCD symptoms when serotonin is increased by serotonin agonists, is that acute stimulation of serotonin receptor subsystems by single-dose 5-HT agonists may be associated with an exacerbation of OCD symptoms, whereas chronic treatment with SSRIs may be associated with adaptive down-regulation of these same serotonin receptor subsystems.

Several lines of evidence also suggest that dysfunction in glutamate neurotransmission may contribute to the pathophysiology of OCD, although the precise abnormality is unknown.[11] An antagonist of the *N*-methyl-D-aspartate glutamate receptor worsens the repetitive behavior of transgenic D1CT-7 mice.[12] Further, preliminary studies suggest that glutamate-modulating drugs like topiramate and riluzole may be effective pharmacologic augmentation strategies for treating OCD.[13–19]

Although SSRIs are considered first-line treatments for OCD,[20] they are often associated with delayed onset of "full" therapeutic effect (often taking 6–12 weeks), only partial symptom reduction, and lack of adequate response or intolerability in 40%–60% of OCD patients. Augmentation with second-generation antipsychotics (dopamine antagonists) has demonstrated efficacy as a second-line treatment,[20] and some anticonvulsants have been reported to help patients as augmentation agents, although the effect is generally small and inconsistently observed.[15,21–25]

Several lines of evidence suggest that dysregulation of excitatory glutamatergic synaptic neurotransmission in the cortico-striato-thalamo-cortical network[26,27] may contribute to the pathophysiology of OCD,[11] as distinct from the monoaminergic hypotheses that underlie established SSRI treatments. Preclinical and neuroimaging studies have

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shown abnormally high glutamatergic concentrations in OCD patients, particularly in the cortico-striato-thalamo-cortical network, and an association between decreased caudate glutamatergic concentrations and reduced OCD symptom severity after SSRI treatment.[11,12,26,28–32] Further, several genes involved in glutamatergic neurotransmission have been implicated in the pathogenesis of OCD in both humans and nonhuman animal models.[20,33–40]

Topiramate is an anticonvulsant that has inhibitory effects on glutamatergic neurotransmission via several mechanisms of action.[41–43] Given the evidence for glutamatergic neurotransmission dysfunction in the pathophysiology of OCD, we hypothesized that topiramate may attenuate the regional cortico-striato-thalamo-cortical hyperactivity seen in OCD patients and be an effective, novel intervention to enhance response to standard SSRI treatment in treatment-resistant OCD.[11] Thus, we conducted the first double-blind, placebo-controlled trial of topiramate augmentation to SSRI treatment for treatment-resistant OCD (for the definition of *treatment-resistant,* see Pallanti et al[44]). Preliminary clinical studies support this hypothesis, as do 2 open-label case series[15,16] and 2 case reports.[17,45] Further, preliminary studies using other antiglutamatergic agents as augmenting drugs (eg, riluzole, *N*-acetylcysteine) support the glutamatergic dysfunction hypothesis.[13,18,19,46] On the other hand, there are 2 case reports of topiramate-induced OCD.[47,48]

METHOD

Thirty-six OCD patients, aged 18–65 years (mean age = 40.5 ± 12.2 years; 28 [78%] women), participated in this multicenter, randomized, double-blind, placebo-controlled, parallel-group study of topiramate augmentation. Patients were recruited and followed up between April 1, 2003, and April 13, 2006. Institutional review board approval was obtained for the study, and the subjects provided written informed consent to participate. Subjects were randomly assigned sequentially as they qualified for the study to receive either topiramate or placebo in a 1:1 ratio according to a computer-generated code. The randomization was balanced using permuted blocks. Subjects and investigators were blinded to treatment assignment. The randomization code was maintained by Ortho-McNeil Pharmaceutical, Inc and was not revealed to study subjects, investigators, or clinical staff until all subjects had completed the study and the database was finalized. The active and placebo study medications were identical in appearance and packaged in identical bottles.

Subjects had a diagnosis of OCD established with the Structured Clinical Interview for *DSM-IV* for Axis I Disorders,[49] onset at least 1 year prior to screening, and a minimum severity of ≥ 18 points on the Yale-Brown Obsessive Compulsive Scale (YBOCS)[50,51] or a minimum score of ≥ 10 on questions 1 through 5 if the subject had only obsessions at visit 2 (baseline). Subjects were in generally good health as confirmed by medical history, baseline psychiatric history, and physical examination. Exclusion criteria included current or recent (within 6 months of the start of study medication) *DSM-IV-TR*[1] diagnosis of substance dependence or abuse (excluding nicotine or caffeine dependence), current or lifetime *DSM-IV-TR* diagnosis of bipolar disorders or psychotic disorders, a history of personality disorder considered by the investigator to likely interfere with assessment or compliance with treatment, current behavioral therapy under medical supervision, a history of seizures, and progressive or degenerative neurologic disorders (eg, multiple sclerosis).

Subjects were randomly assigned to a topiramate group (n = 18, mean age = 42.5 ± 11.8 years, male:female ratio = 3:13) or a placebo group (n = 18, mean age = 38.4 ± 12.6 years, male:female ratio = 5:13) in this 12-week trial with a washout/screening visit up to 1 month before the start of the trial. Subjects had been taking the maximum SSRI dose they could tolerate for at least 12 weeks (1 was missing baseline SSRI information) and their current dose for at least 6 weeks, which was maintained throughout the course of the study. Subjects were not taking psychotropic medications other than an SSRI at the start of the study.

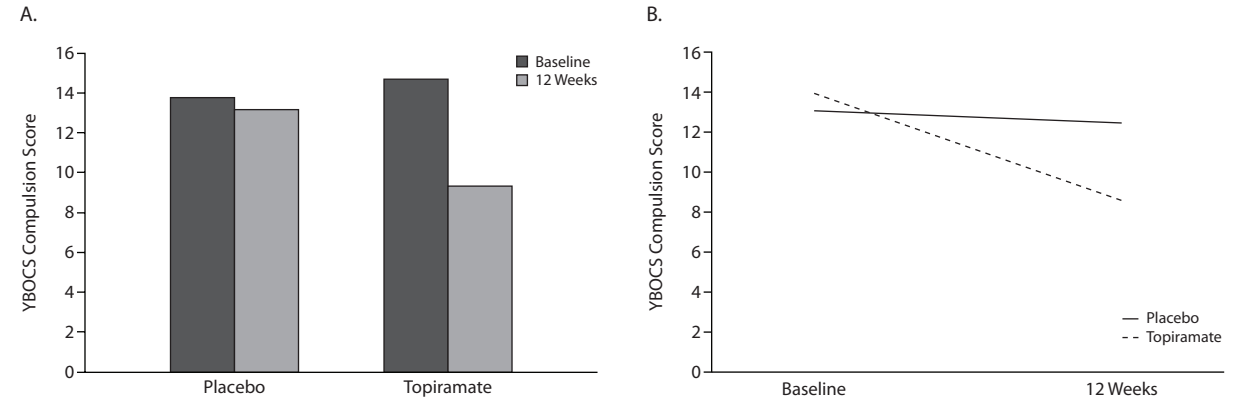
The subjects were seen and assessed at 9 time points (washout/screen, baseline, and weeks 1, 2, 4, 6, 8, 10, and 12). The washout data were not used in the analyses. Study medication was titrated over 8 weeks up to 400 mg/d or the maximum tolerated dose (study medication consisted of either 25 or 100 mg of topiramate, or matching placebo, in identically appearing tablets; totaling 1–4 tablets per day depending on the dose. After the titration period, the dose remained stable for the 4-week maintenance period. At the completion of the maintenance period, subjects were tapered off study medication over 1 week. Subject participation could be terminated at any time for lack of efficacy, subject choice, protocol violation (eg, noncompliance), or adverse event or if the subject was lost to follow-up.

The primary outcome measures were changes in the YBOCS total score and in the compulsions and obsessions subscores. Secondary outcome measures were changes in scores from the Montgomery-Asberg Depression Rating Scale,[52] Clinical Global Impressions Scale (CGI),[53] Patient Global Impressions Scale,[53] and Sheehan Disability Scale.[54] We used mixed regression models to test the time (coded as weeks) × treatment (coded as placebo = 0, treatment = 1) interaction and analyzed all 36 randomized patients using intent-to-treat analysis (36/36, or 18/18 in each group).

RESULTS

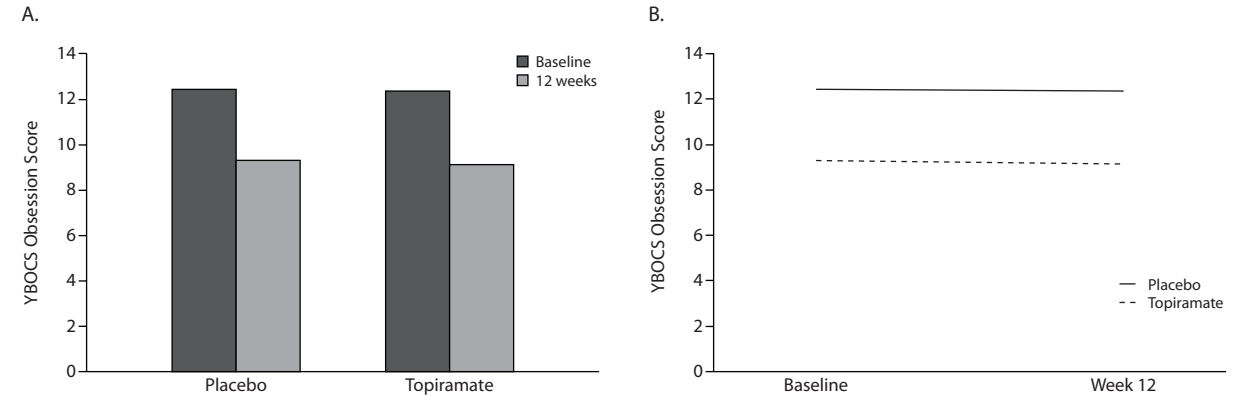
The mean maximum dose of topiramate achieved in the active drug group was 206.9 ± 126.0 mg/d (range, 75–400 mg/d), and the mean endpoint dose was 177.8 ± 134.2 mg/d (range, 50–400 mg/d). The mean maximum dose of placebo achieved in the placebo group was 311.1 ± 144.1 mg/d (range, 25–400 mg/d), and the mean endpoint dose was 305.6 ± 150.1 (range, 25–400 mg/d). There were 27 completers and 9 dropouts. Of the subjects randomly assigned to topiramate, 5 (28%) were taken off treatment with the drug completely due to adverse events. Of the placebo subjects, 4

Figure 1. Predicted Scores at Baseline and 12 Weeks (A) and Predicted Linear Change (B) on the YBOCS Compulsions Subscale for Placebo and Topiramate Groups From the Mixed Regression Model[a]



[a]There was a significant ($P = .014$) time-by-treatment interaction.
Abbreviation: YBOCS = Yale-Brown Obsessive Compulsive Scale.

Figure 2. Predicted Scores at Baseline and 12 Weeks (A) and Predicted Linear Change (B) on the YBOCS Obsessions Subscale for Placebo and Topiramate Groups From the Mixed Regression Model[a]



[a]There was an overall significant decrease in obsessions across the 12 weeks ($P = .01$), but a nonsignificant ($P = .99$) time-by-treatment interaction.
Abbreviation: YBOCS = Yale-Brown Obsessive Compulsive Scale.

(22%) were taken off the drug: 2 (11%) due to "lack of efficacy," 1 (6%) due to "subject choice," and 1 (6%) due to a protocol violation. Seven (39%) topiramate subjects had their dosage reduced due to adverse events, compared to only 3 (17%) placebo subjects. All subjects and available data were included in the primary mixed-effects regression analysis.

At baseline, the treatment groups did not differ on any of the primary, secondary, or demographic variables (except for race, which we adjusted for and which did not affect the results). The mean baseline YBOCS scores for the placebo group were total score, 26.4 ± 5.1; obsessions, 13.1 ± 3.1; and compulsions, 13.3 ± 2.5. The mean baseline YBOCS scores for the topiramate group were total score, 25.9 ± 4.6; obsessions, 12.6 ± 2.6; and compulsions, 13.4 ± 2.5. There was a significant treatment effect on the YBOCS compulsions ($t = 2.60$, $P = .014$) subscale (Figure 1A). Over the 12 weeks of the trial, the topiramate group showed an estimated average linear decrease of 5.38 points compared to only 0.6 points for the placebo group (Figure 1B). The difference in the decrease between groups was 4.78 points. The effect size (average differential decrease in the treatment group compared to control group per week) was −0.33 with a 95% confidence interval of −0.58 to −0.07. The 13 topiramate completers experienced an average decrease of 4.8 points on the YBOCS compulsions subscale compared to 2.5 points for the 14 placebo completers. The difference in the decrease between groups was 2.3 points. Thus, the completers in both groups showed a stronger effect than the intent-to-treat groups, but the difference in change scores between the groups was about the same. The *P* value for the completer analysis on change in compulsions was .252. There was no significant treatment effect on the YBOCS obsessions ($t = .002$, $P = .99$) subscale (Figure 2, parts A and B) or the YBOCS total score ($t = 1.64$, $P = .11$) (Figure 3, parts A and B) and no evidence of differential response between the topiramate and placebo groups on any of the secondary measures.

There was no relationship between the characteristics of the adverse events (eg, severity) and treatment group (Table 1). However, topiramate subjects experienced significantly more of the following known associated adverse events than placebo subjects: influenza-like symptoms ($P = .02$), paresthesia ($P = .001$), difficulty with memory not otherwise

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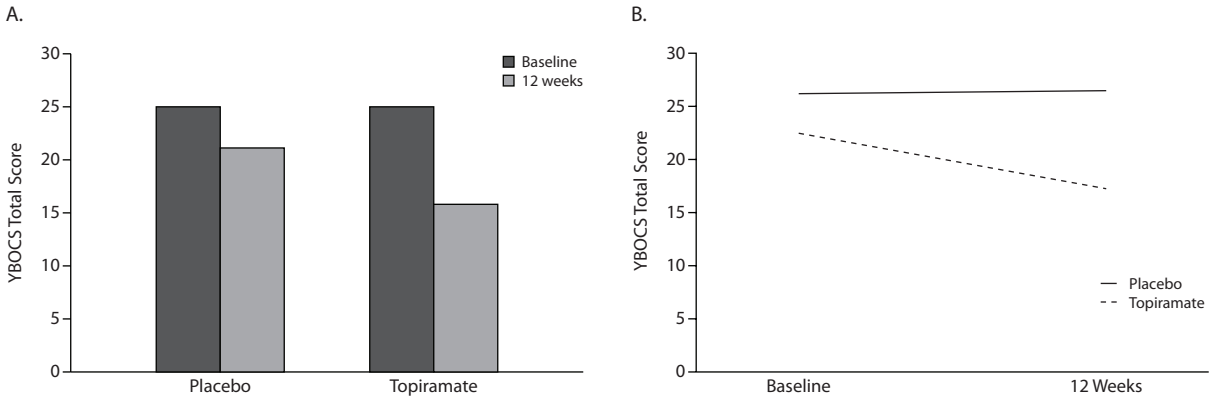
Figure 3. Predicted Scores at Baseline and 12 Weeks (A) and Predicted Linear Change (B) on the YBOCS Total Score for Placebo and Topiramate Groups From the Mixed Regression Model[a]



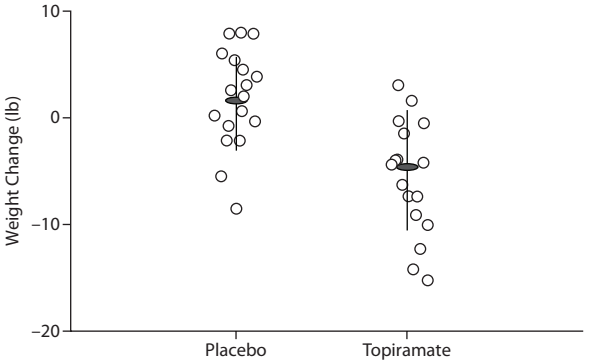
[a]The time-by-treatment interaction was nonsignificant ($P = .11$).
Abbreviation: YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 1. Adverse Events Occurring in ≥ 15% of Patients Receiving Topiramate (n = 18) or Placebo (n = 18)

Event	Topiramate, n (%)	Placebo, n (%)	*P* Value[a]
Body as a whole—general			
Fatigue	6 (33.33)	2 (11.11)	.11
Influenza-like symptoms	5 (27.78)	0 (0)	.02*
Central and peripheral nervous system			
Paresthesia	8 (44.44)	0 (0)	.001*
Headache	1 (5.56)	3 (16.67)	.30
Dizziness	3 (16.67)	1 (5.56)	.30
Gastrointestinal system			
Toothache	3 (16.67)	0 (0)	.11
Psychiatric disorders			
Anxiety	0 (0)	3 (16.67)	.11
Difficulty w/memory NOS	4 (22.22)	0 (0)	.05*
Insomnia	5 (27.78)	3 (16.67)	.35
Somnolence	4 (22.22)	6 (33.33)	.36
Respiratory system disorders			
Respiratory disorder	5 (27.78)	9 (50)	.15
Sensory disturbances			
Taste perversion	4 (22.22)	0 (0)	.05*

[a]Fisher exact test.
*$P \leq .05$.
Abbreviation: NOS = not otherwise specified.

Figure 4. Comparison of Placebo and Topiramate Groups on Weight Change[a,b]



[a]Mean (SD) values: placebo, 1.8 (4.4) kg; topiramate, –5.5 (5.2) kg.
[b]These results were winsorized to reduce the effect of an extreme outlier (–30) in the treatment group.

specified ($P = .05$), and taste perversion ($P = .05$). No new or unexpected adverse events occurred. There was a substantial and statistically significant difference between groups in weight change over the course of the study ($t = 4.04$, $P < .001$) (Figure 4). The topiramate group lost an average of 5.5 lb, whereas the placebo group gained an average of 1.8 lb. Fifteen of the 18 (83%) topiramate subjects lost weight, compared with only 7 of the 18 (39%) placebo subjects (Fisher exact test, $P = .015$). The topiramate subjects were 7.9 times more likely to lose weight than the placebo subjects.

DISCUSSION

Compared to the placebo group, the topiramate augmentation group exhibited a significantly greater decrease in YBOCS compulsions over the 12-week study period. However, the groups did not differ on YBOCS obsessions or total scores. The results of this first double-blind, placebo-controlled trial of topiramate augmentation of SSRI treatment for treatment-resistant OCD suggest that topiramate may be beneficial for compulsions, but not obsessions. Given our modest sample size and study duration, further studies are needed.

The 2 previous open-label trials and 2 case reports of topiramate treatment of OCD did not find improvements in compulsions alone. However, Rubio et al[16] found that compulsions improved first, and obsessive thoughts benefited from therapy later. Hollander and Dell'Osso[17] found that while their patient's obsessions and compulsions started to improve at the same time, compulsions showed a more consistent improvement in the first weeks of treatment. Van Ameringen and colleagues[15] used the CGI as their primary outcome measure and so did not analyze improvements in obsessions and compulsions separately. Vinkers and van der Wee's[45] patient had only obsession at baseline (which improved with topiramate) and did not have compulsions. Obsessions may take longer to improve with topiramate or may simply be more amenable to cognitive therapy. Further,

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the lower mean endpoint dose in this study (177.8 ± 134.2 mg/d) than in the earlier open-label trials (253.1 ± 93.9 mg/d,[15] 237.5 ± 29.1 mg/d[16]) that suggested greater effectiveness may account in part for the limited treatment response observed.

Topiramate was not well tolerated in this study: 28% of subjects discontinued the drug for adverse events compared to 0% taking placebo, and 39% required a dose reduction for this reason versus 17% taking placebo. However, topiramate was associated with significant weight loss. This contrasts with the standard augmentation strategy with antipsychotic agents, which is associated with significant weight gain.[55] In view of the large percentage of OCD patients who do not respond to SSRI treatment and the unwanted side effects of the most commonly utilized augmentation strategy (adding an atypical antipsychotic drug), the results of this trial and of the earlier open-label study[15] suggest that topiramate augmentation may be reasonably considered for OCD patients inadequately responsive to SSRIs. However, it should be noted that only 1 of 3 primary outcome measures (YBOCS compulsions score) indicated significant therapeutic effect. Thus, we found only suggestive evidence of a possible effect, and further investigation is needed.

The neurochemical mechanism that may underlie the topiramate-associated improvement in compulsions in SSRI-resistant OCD patients remains to be elucidated. However, we speculate that modifications in glutamatergic function may be responsible, at least in part. This speculation is consistent with the idea that glutamatergic dysfunction may be involved in OCD pathophysiology. However, more than 1 neurotransmitter problem is likely to be involved in OCD pathophysiology, an idea supported by the clear efficacy of SSRIs and clomipramine in treating the disorder and by preliminary imaging, clinical trial, and animal model data. Serotonin may, in fact, act as a modulator of glutamate- and GABA-mediated neurotransmission.[56]

Drug names: clomipramine (Anafranil and others), riluzole (Rilutek and others), sumatriptan (Imitrex, Sumavel, and others), topiramate (Topamax).

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Potential conflicts of interest: **Dr Koran** chaired the American Psychiatric Association (APA) Workgroup that wrote the Practice Guideline for OCD; has received research grants from Eli Lilly, Forest, Ortho-McNeil Neurologics, and Somaxon; and is on the speakers bureau for Forest. **Dr Shapira** is named on a patent application (No. 11/830,906) relating to this study. **Dr Hollander** received research grants from and has been a consultant for Ortho-McNeil Janssen and served on the APA Workgroup that wrote the Practice Guideline for OCD and on the *DSM-V* Anxiety Disorders workgroup. **Drs Berlin, Jenike, Chaplin,** and **Pallanti** report no biomedical financial interests or potential conflicts of interest.

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