Tics Moderate Treatment Outcome with Sertraline but not Cognitive-Behavior Therapy in Pediatric Obsessive-Compulsive Disorder

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Background: *The presence of a comorbid tic disorder may predict a poorer outcome in the acute treatment of pediatric obsessive-compulsive disorder (OCD).*

Methods: *Using data from the National Institute of Mental Health (NIMH)-funded Pediatric OCD Treatment Study (POTS) that compared cognitive-behavior therapy (CBT), medical management with sertraline (SER), and the combination of CBT and SER (COMB), to pill placebo (PBO) in children and adolescents with OCD, we asked whether the presence of a comorbid tic disorder influenced symptom reduction on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) after 12 weeks of treatment.*

Results: *Fifteen percent (17 of 112) of patients exhibited a comorbid tic disorder. In patients without tics, results replicated previously published intent-to-treat outcomes: COMB > CBT > SER > PBO. In patients with a comorbid tic disorder, SER did not differ from PBO, while COMB remained superior to CBT and CBT remained superior to PBO.*

Conclusions: *In contrast to CBT outcomes, which are not differentially impacted, tic disorders appear to adversely impact the outcome of medication management of pediatric OCD. Children and adolescents with obsessive-compulsive disorder and a comorbid tic disorder should begin treatment with cognitive-behavior therapy alone or the combination of cognitive-behavior therapy plus a serotonin reuptake inhibitor.*

Key Words: Pediatric, OCD, treatment, tic disorders

At any given time, between one half and one percent of children and adolescents suffers from clinically significant obsessive-compulsive disorder (OCD) (Flament et al 1988), giving it roughly the same cross-sectional prevalence as juvenile-onset diabetes.

We recently published intent-to-treat results from the Pediatric OCD Treatment Study (POTS 2004), which is the first randomized controlled trial to directly compare the efficacy of an established medication (sertraline; SER), OCD-specific cognitive-behavior therapy (CBT), and their combination (COMB) to a control condition, pill placebo (PBO), in the acute treatment of pediatric OCD. All three active treatments proved superior when compared to placebo. When compared to each other, combined treatment proved superior to CBT and to sertraline, which did not differ from one another. Fifty-four percent of the patients who received combined treatment and 39% of those who received CBT alone achieved clinical remission, in comparison to approximately 21% of those who received sertraline and 3% who received placebo.

One question of paramount interest to clinicians and to researchers attempting to refine and improve treatment outcomes is "which treatment for which child with what characteristics?"

In a series of papers, Geller and colleagues have suggested that the presence of a tic disorder is one of the defining characteristics of an early onset subtype of OCD in youth (Geller et al 1998, 2001). Comorbidity with tic disorders is commonly cited as a poor prognostic factor for both medication and CBT (Leonard et al 1993). In adults, tic disorders have been given as a reason for neuroleptic augmentation of treatment with a serotonin reuptake inhibitor (McDougle et al 1993), although the only randomized controlled trial of neuroleptic augmentation in adults did not demonstrate a moderating effect for tics (McDougle et al 2000). While one study in children and adolescents with OCD found that comorbidity did not adversely impact the outcome of treatment with sertraline relative to PBO (March et al 1998), another study of paroxetine versus placebo found that the presence of tics was associated with a poorer response to paroxetine (Geller et al 2003). No studies have examined the moderating effects of tics on CBT outcomes in adult or pediatric OCD.

Fifteen percent of the POTS sample exhibited a comorbid tic disorder providing an opportunity to evaluate the extent to which the presence of a comorbid tic disorder influences response to treatment. In this paper, we report an analysis of the main and moderating effects of a comorbid tic disorder on acute treatment outcome at 12 weeks. We hypothesized that tics would exert an overall adverse effect on outcome, and that this effect would unfavorably impact CBT and sertraline more than the combined treatment condition.

Methods and Materials

The background and rationale, sample and primary intent-to-treat outcomes for the POTS have been described elsewhere (Franklin et al 2003; POTS 2004) Funded by the National Institute of Mental Health (NIMH) and approved by the institutional review boards (IRBs) at each of the three participating sites, POTS is a multicenter randomized clinical trial designed to evaluate the relative benefit and durability of four treatments for children and adolescents with OCD: (1) SER, (2) CBT; (3) COMB; and (4) PBO. All patients and at least one of their parents

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provided written informed consent, and the institutional review board approved the protocol at each site.

A volunteer sample of 112 subjects between the ages of 7-17 inclusive with a primary DSM-IV diagnosis of OCD entered the study; the sample was evenly split between males and females, and approximately equal with respect to adolescents ages 12-17 and younger children ages 7-11.

Patients assigned to medical management with SER or PBO ("pills only") had one child and adolescent psychiatrist throughout the study who, in addition to monitoring clinical status and medication effects, offered general support and encouragement to resist OCD. Patients were seen weekly for medication adjustment based on a standardized escalating dose titration schedule during the first six weeks of Phase I, then every other week until the end of Phase I for a total of 9 visits over 12 weeks. The titration schedule used a fixed flexible upward titration from 25 to 200 mg over six weeks, after which the dose could be adjusted as a function of side effects only. The CBT Treatment Manual was adapted from published work (March and Mulle 1998) that is widely acknowledged as representing the standard of care (Franklin et al 2002; King et al 1998) CBT consisted of 14 visits over 12 weeks that involved: (1) psychoeducation, (2) cognitive training, (3) mapping OCD target symptoms, and (4) exposure and response (ritual) prevention.

Consistent with an intent-to-treatment analytic model, all patients, regardless of responder status, returned for all scheduled assessments. The primary dependent measure was the Children's Yale-Brown OC Scale (CY-BOCS) administered by an independent evaluator blind to treatment status at baseline and weeks 4, 8, and 12. The CYBOCS assesses obsessions and compulsions separately over five dimensions: time consumed, distress, interference, degree of resistance, and control (Scahill et al 1997b) Tic and other comorbid disorders were assessed using the Anxiety Disorders Interview Schedule for Children (ADIS-C; Silverman and Nelles 1988) modified to include the Yale Global Tic Severity Scale (Leckman et al 1989), which has recently been shown to have acceptable psychometric properties in children and adolescents (Storch et al 2005).

The primary outcome for the predictor/moderator analyses is a week 12 predicted score on the CY-BOCS derived from the same linear mixed effect "random regression" (RR) (Gueorguieva and Krystal 2004; Weinfert 2000) model used in the POTS intent-to-treat analyses. Specifically, the impact of treatment at week 12 was modeled as a linear function of fixed effects for treatment, site, and days since baseline (linear time trend) and all significant two and three way interactions. For the purpose of this paper, we used the general linear model approach to examine the main and interaction effects of treatment and presence of a comorbid tic disorder on the week 12 predicted scores. To be consistent with the primary efficacy analysis, site (Duke and Penn/Brown collapsed) was included as a covariate to adjust for possible site effects. Following Kraemer (Kraemer et al 2002), a significant tic disorder x treatment interaction effect on outcome indicates that the variable is a moderator. A significant main effect of tic disorder on outcome but a nonsignificant tic disorder x treatment interaction would indicate that tic disorder is a predictor of overall outcome, but does not differentially impact (moderate) outcome by treatment condition. Because these analyses were considered exploratory rather than confirmatory, the traditional alpha level of .05 was used for all statistical tests. Analyses of baseline characteristics used standard parametric and nonparametric statistical procedures. Statistical analyses were performed using SAS 9.1 software (SAS Institute, Cary, North Carolina).

Results

Seventeen of 112 patients (15.2%) exhibited either Tourette's Syndrome or a chronic motor tic disorder. No patient had vocal tics only. The mean (SD) CY-BOCS score at baseline did not differ ($p < .95$) for patients with (M = 24.7; SD = 4.7) or without (M = 24.6; SD = 3.9) a tic disorder, and there were there were no differences in the frequency of tic disorders at baseline by treatment group or by site. Patients with a tic disorder did not differ from those without a tic disorder with respect to gender, but were slightly younger (Mean (SD) = 10 (1.8) vs. 12.0 (2.7) $p < .006$). As expected, differences in pattern of comorbidity were present though not statistically significant. Forty-one percent of patients with a tic disorder and 55% of patients without a tic disorder had at least one comorbid internalizing disorder (Fisher's Exact $p < .06$). Forty-seven percent of patients with a tic disorder and 18% of patients without a tic disorder had at least one comorbid externalizing disorder (Fisher's Exact $p < .07$).

Using the predicted week 12 CY-BOC score as the dependent variable, a 2 (site) x 4 (treatment) x 2 (tic status) multivariate analysis of variance yielded a main effect for site (Wald $X^2 = 3.88$, $p < .05$) and for treatment (Wald $X^2 = 127.01$, $p < 001$). Combined treatment ($p < .001$), CBT ($p < .001$) and SER ($p < .01$) proved superior to PBO; COMB was superior to CBT ($p < .001$) and to SER ($p < .001$); and CBT was superior to SER ($p < .002$). Controlling for tic disorder and site, these analyses replicated the previously published intent-to-treat outcomes, which were ordered as follows: COMB > CBT > SER > PBO (POTS 2004).

Table 1 depicts the mean (SD) for the CY-BOCS score at baseline and the mean (SD, 95% confidence intervals) for the week 12 adjusted CY-BOCS score stratified by treatment group and by the presence or absence of a tic disorder. The post-treatment CY-BOCS score mean (SD) for patients without a tic disorder was slightly lower with (15.5 (5.3)) than without (17.0 (5.6)) a tic disorder, but the main effect of tic disorder was not statistically significant (Wald $X^2 = 1.21$, $p < .05$) where the tic disorder treatment interaction term was statistically significant ($X^2 = 12.32$, $p < .006$). To explore the origin of the significant interaction, we repeated the between-group post-hoc contrasts at each level of the tic disorder moderator. Only the comparison between SER and PBO showed a statistically significant shift in the presence of a comorbid tic disorder. Specifically, in the presence of a tic disorder, SER did not differ from PBO ($p < .56$) whereas in the absence of a tic disorder SER proved superior to PBO ($p < .001$). Hence, the tic disorder * treatment interaction appears to arise from a reduction in magnitude of the impact of SER on OCD symptoms in the presence of tics.

Discussion

Replicating earlier results from a randomized controlled trial of paroxetine in pediatric OCD (Geller et al 2003), sertraline proved statistically superior to placebo only in patients without tics. Hence, in contrast to the hypothesis that tics would exert an overall adverse effect on OCD outcome, and that this effect would unfavorably impact CBT and sertraline more than the combined treatment condition, the data suggest that when a comorbid tic disorder is present, patients treated with CBT either alone or in combination with a serotonin reuptake inhibitor will

Table 1. CY-BOCS Scores at 12 Weeks by Treatment Group and Tic Disorder Status[a]

Treatment Group	*n*	Baseline Mean (SD)	Wk 12 Mean (SD)	95% Confidence Limits Wk 12 Mean	
PBO - Tic	23	25.52 (3.39)	21.88 (2.97)	20.67	23.11
PBO + Tic	5	23.8 (2.68)	20.42 (2.99)	17.80	23.04
SER - Tic	23	23.04 (3.98)	15.90 (3.02)	14.67	17.13
SER + Tic	5	25.8 (7.49)	21.02 (3.06)	18.34	23.70
CBT - Tic	25	26.12 (4.61)	14.14 (3.00)	12.97	15.31
CBT + Tic	3	25.00 (6.24)	15.51 (3.03)	12.08	18.94
COMB - Tic	24	23.75 (3.11)	10.12 (2.98)	8.93	11.32
COMB + Tic	4	24.25 (2.22)	8.63 (3.00)	5.690	11.57

CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; PBO, placebo; SER, sertraline; CBT, cognitive-behavior therapy; COMB, combination of CBT and SER; RRM, random regression model.

[a]Baseline Mean (SD) is unadjusted; Wk 12 score mean (SD) represents RRM predicted score at 12 weeks.

show a substantially higher probability of improvement in OCD than will patients treated with medication alone.

The mechanism for this effect is unclear. While low cell frequencies in the tic disorder group preclude segmenting the tic disorder moderator variable or examining mediational (mechanism) effects, it is possible, perhaps even reasonable, to assume that CBT exhibited greater activity in patients with both OCD and tics. Perhaps those children with tic-like OCD ("just so" obsessions, tapping rituals) improved more with CBT than with medications? In support of this hypothesis, SSRIs are not generally considered effective treatments for tics (Scahill et al 1997a), whereas exposure and response prevention has been used to successfully modify tics that resemble compulsions (Woods et al 2000) Alternatively, the broad strategy in CBT of calmly and skillfully responding to the arising of OCD symptoms may have generalized from OCD to tics, which were not specifically targeted in CBT. CBT also may have benefited patients with tics indirectly through an impact on externalizing disorders, which were slightly more common in patients with than without tics.

Low cell frequencies for excellent responders precluded further analysis of the impact of tics on the probability of clinical remission. Only 3 of 17 (17%) patients with a tic disorder as contrasted to 30 of 95 (32%) of patients without a tic disorder met CY-BOCS criteria (CY-BOCS $\leq$ 10) for clinical remission (Fisher's Exact $p < .38$). It is interesting to speculate, given a nonsignificant trend toward overall poor response in the presence of a tic disorder, and the substantially greater prevalence of comorbid externalizing disorders in children with tic disorder, that the presence of a tic disorder does in fact represent a poor prognosis factor as suggested by Leonard et al (1993), and that this study is insufficiently powered to detect this effect.

The clinical implications of the POTS results, which would benefit from replication in sample stratified for the presence of a tic disorder, are reasonably straightforward. Tic disorders do not adversely impact CBT or CBT plus medications, which show larger effect sizes than medication management alone independent of the pattern of comorbidity. Conversely, tic disorders appear to adversely impact the outcome of medication management alone. Hence, children and adolescents with obsessive-compulsive disorder plus a comorbid tic disorder should begin treatment with cognitive-behavior therapy alone or the combination of cognitive-behavior therapy plus a serotonin reuptake inhibitor. These findings support the overall recommendation made in the initial POTS report (2004) that CBT be considered an essential component (from the standpoint of informed consent if not yet a standard of care) in the treatment of pediatric OCD.

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