Cognitive-Behavior Therapy, Sertraline, and Their Combination for Children and Adolescents With Obsessive-Compulsive Disorder
The Pediatric OCD Treatment Study (POTS) Randomized Controlled Trial

The Pediatric OCD Treatment Study (POTS) Team

EPIDEMIOLOGIC DATA SUGGEST that approximately 1 in 200 young people has obsessive-compulsive disorder (OCD), which in many cases severely disrupts academic, social, and vocational functioning.[1] Among adults with OCD, one third to one half developed the disorder during childhood or adolescence,[2] which suggests that early intervention in childhood may prevent long-term morbidity in adulthood.

The efficacy of pharmacotherapy with a serotonin reuptake inhibitor (SRI) for pediatric OCD has been established for clomipramine,[2] fluvoxamine,[3] sertraline,[4] and fluoxetine.[5] The pediatric literature[6] is consistent with the adult literature[7] in revealing a 30% to 40% reduction in OCD symptoms with pharmacotherapy, which leaves the great majority of patients who respond to medication management alone with clinically significant residual symptoms.

Cognitive-behavior therapy (CBT) is a well-documented intervention for adults with OCD.[8] Prospective open-label studies also suggest the potential usefulness of CBT for pediatric OCD.[9,10] One direct comparison of CBT vs the SRI clomipramine for pediatric OCD found an advantage for CBT,[11] but to date there are no published studies

Context The empirical literature on treatment of obsessive-compulsive disorder (OCD) in children and adolescents supports the efficacy of short-term OCD-specific cognitive-behavior therapy (CBT) or medical management with selective serotonin reuptake inhibitors (SSRIs). However, little is known about their relative and combined efficacy.

Objective To evaluate the efficacy of CBT alone and medical management with the selective serotonin reuptake inhibitor sertraline alone, or CBT and sertraline combined, as initial treatment for children and adolescents with OCD.

Design, Setting, and Participants The Pediatric OCD Treatment Study, a balanced, masked randomized controlled trial conducted in 3 academic centers in the United States and enrolling a volunteer outpatient sample of 112 patients aged 7 through 17 years with a primary *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of OCD and a Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) score of 16 or higher. Patients were recruited between September 1997 and December 2002.

Interventions Participants were randomly assigned to receive CBT alone, sertraline alone, combined CBT and sertraline, or pill placebo for 12 weeks.

Main Outcome Measures Change in CY-BOCS score over 12 weeks as rated by an independent evaluator masked to treatment status; rate of clinical remission defined as a CY-BOCS score less than or equal to 10.

Results Ninety-seven of 112 patients (87%) completed the full 12 weeks of treatment. Intent-to-treat random regression analyses indicated a statistically significant advantage for CBT alone ($P=.003$), sertraline alone ($P=.007$), and combined treatment ($P=.001$) compared with placebo. Combined treatment also proved superior to CBT alone ($P=.008$) and to sertraline alone ($P=.006$), which did not differ from each other. Site differences emerged for CBT and sertraline but not for combined treatment, suggesting that combined treatment is less susceptible to setting-specific variations. The rate of clinical remission for combined treatment was 53.6% (95% confidence interval [CI], 36%-70%); for CBT alone, 39.3% (95% CI, 24%-58%); for sertraline alone, 21.4% (95% CI, 10%-40%); and for placebo, 3.6% (95% CI, 0%-19%). The remission rate for combined treatment did not differ from that for CBT alone ($P=.42$) but did differ from sertraline alone ($P=.03$) and from placebo ($P<.001$). CBT alone did not differ from sertraline alone ($P=.24$) but did differ from placebo ($P=.002$), whereas sertraline alone did not ($P=.10$). The 3 active treatments proved acceptable and well tolerated, with no evidence of treatment-emergent harm to self or to others.

Conclusion Children and adolescents with OCD should begin treatment with the combination of CBT plus a selective serotonin reuptake inhibitor or CBT alone.

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comparing CBT, pharmacotherapy with a selective serotonin reuptake inhibitor (SSRI), and their combination with a control group in the same patient population.

The purpose of the present study, which was funded by the National Institute of Mental Health (NIMH), was to evaluate the efficacy of CBT alone, medication management with the SSRI sertraline alone, or a combined treatment consisting of CBT and sertraline as initial treatment for children and adolescents with OCD.

METHODS

The rationale, design, and methods for the Pediatric OCD Treatment Study (POTS) have been described in detail elsewhere.[12] Briefly, POTS stage 1 consists of a 12-week multicenter, randomized, parallel-group clinical trial designed to evaluate the relative benefit and durability of 4 treatments for children and adolescents with OCD: (1) CBT alone; (2) medical management with sertraline, (3) combined treatment consisting of CBT and sertraline, and (4) a control condition, pill placebo. A CBT plus placebo group, which would have controlled for drug expectancy effects when comparing CBT alone with combined treatment, was deemed to be too costly and to lack ecological validity.

Consistent with an intent-to-treat analytic model, all patients, regardless of responder status, were asked to return for all scheduled assessments. An independent evaluator who was kept masked to treatment status assessed the primary efficacy end points. Responders to 1 of the 3 active treatments in stage 1 were eligible to enter a 16-week stage 2 treatment discontinuation study, which will be reported separately. At the point they exited stage 1, all patients receiving placebo were offered their choice of CBT, medication, or the combination of CBT and sertraline, depending on patient preference and end-of-treatment status.

Participants

A volunteer sample of 112 outpatients aged 7 through 17 years with a pri-

mary *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*)[13] diagnosis of OCD balanced by site and treatment condition entered the study between September 1997 and December 2002. Three sites participated in the study: Duke University, the University of Pennsylvania (Penn) and, under a subcontract to Penn, Brown University. Patients were recruited primarily through clinical referral from mental health clinicians and primary care physicians and by advertising in print and radio media. All patients and at least 1 of their parents provided written informed consent, and the protocol was approved by the institutional review board at each site.

To facilitate accrual of a patient sample representative of treatment-seeking pediatric patients with OCD, inclusion and exclusion criteria were kept to a minimum. Inclusion criteria were receiving treatment as an outpatient; aged 7 through 17 years; *DSM-IV* diagnosis[13] of OCD ascertained jointly on the Children's Yale-Brown Obsessive-Compulsive Scale[14] (CY-BOCS) and the Anxiety Disorders Interview Schedule for Children[15] (ADIS-C); a CY-BOCS total score greater than 16; NIMH Global Severity Score[16] greater than 7, indicating clinically significant impairment due to OCD; IQ greater than 80 extrapolated from block design and vocabulary subtest scores (raw score ≥ 6) on the Wechsler Intelligence Scale for Children[17]; and being free of antiobsessional medications prior to the start of the study.

Exclusion criteria ascertained on the ADIS-C were the presence of major depression or bipolar illness; primary diagnosis of Tourette disorder; any pervasive developmental disorder; psychosis; concurrent treatment with psychotropic medication or psychotherapy outside study; 2 previous failed SRI trials for OCD or a failed trial of CBT for OCD; intolerance to sertraline; any medical or neurologic disorder that posed a contraindication to one of the study treatments or that would interfere with the study assessment protocol; and pregnancy. To avoid prese-

lection biases favoring one treatment condition over another, we also excluded children treated previously with medication, CBT, or their combination who experienced complete or nearly complete remission of symptoms (defined as an end-of-treatment CY-BOCS score <6 by retrospective rating). To enhance generalizability, patients with attention-deficit/hyperactivity disorder (ADHD) who had been stably medicated with a psychostimulant for 3 consecutive months were deemed study eligible. Female patients of childbearing status were required to use birth control if sexually active.

Study entry typically required 2 to 3 (range, 1-6) weeks and proceeded through 4 entry gates: (1) telephone screening, (2) review of patient- and parent-report measures, (3) consent and assessment of all inclusion and exclusion criteria, and (4) baseline assessment and randomization to treatment. Patients were randomly assigned (within-site) to treatment using a computer-generated randomized permuted blocking procedure[18] using a block size of 4. Randomization was considered to have occurred when treatment assignment was revealed. All randomly assigned patients were included in the intent-to-treat analyses.

Concealment methods followed standard recommendations; no between-treatment group differences at baseline or evidence of statistically identifiable selection biases were apparent.[19] We tested whether there was any selection bias in treatment assignment by examining the probability of each condition within each randomized block (ie, 0.25 for the first condition in the block and 1.0 for the fourth condition within the block) and tested whether these probabilities interacted with time, treatment condition, and site to predict outcome. No evidence for selection bias was found ($F_{3,281}=0.06$, $P=.98$).

Except in emergencies, participants and clinicians remained masked in the pills-only conditions (ie, sertraline alone and matching placebo). For reasons of

ecological validity and pragmatic considerations involving cost and ease of patient accrual,[12] patients and clinicians were aware that participants in the combined-treatment group received active medicine and that patients receiving CBT received no medication. As is necessary in studies comparing psychosocial and pharmacological interventions, masking was maintained for the primary dependent measures by means of an independent evaluator.

Interventions

Patients assigned to medical (ie, pills only) management with sertraline or placebo had 1 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. Psychotherapy procedures specifically targeting OCD were prohibited. Patients were seen weekly for medication adjustment based on a standardized escalating dose titration schedule during the first 6 weeks of stage 1, then every other week until the end of stage 1 for a total of 9 visits over 12 weeks. The titration schedule used a fixed flexible upward titration from 25 mg/d to 200 mg/d over 6 weeks, after which the dosage could be adjusted as a function of adverse effects only. Except for the first visit, which typically lasted 50 minutes so that the psychiatrist could review the rationale for treatment, all pharmacotherapy visits lasted approximately 30 minutes. Parents completed a medication diary and pill counts to assess medication compliance at each visit. Dosage increases were delayed or dosages reduced for clinically significant adverse effects, eg, those producing distress and dysfunction for which the clinician and the patient or parent believed dosage reduction was indicated.

The CBT treatment manual was adapted from published work[20] that is widely acknowledged as representing the standard of care.[21,22] The CBT regimen consisted of 14 visits over 12 weeks and involved (1) psychoeducation, (2) cognitive training, (3) mapping OCD target symptoms, and (4) exposure and response (ritual) prevention. Except for weeks 1 and 2, during which patients were seen twice weekly, visits were conducted on a weekly basis and lasted approximately 1 hour. Each session included a statement of goals, review of the previous week, provision of new information, therapist-assisted practice, homework for the coming week, and monitoring procedures. Sessions 1, 7, and 11 included parents for the entire session. By design, the CBT manual provided sufficient flexibility to accommodate the developmental stage of the child and to address maladaptive parent-child interactions resulting from the child's OCD.

For patients in the combined-treatment group, CBT and medication management began simultaneously according to procedures specified in the CBT and pharmacotherapy manuals. CBT and medication visits were time-linked to reduce inconvenience for patients or parents and to increase compliance. Both CBT and medication management were conducted according to protocols that independently escalated the intensity of treatment over time so that changes in the nature or intensity of CBT and medication management did not depend on the other treatment.

Diagnostic and Primary Outcome Measures

All patients were assessed at baseline and at weeks 4, 8, and 12 by the same independent evaluator masked to treatment status. Diagnostic status for OCD and comorbidity were assessed using the research diagnostic version of the ADIS-C modified to include information from the CY-BOCS. The CY-BOCS, which assesses obsessions and compulsions separately over 5 dimensions (time consumed, distress, interference, degree of resistance, control), is a clinician-rated instrument that merges data from clinical observation and parent and child report. As the primary scalar outcome variable, the CY-BOCS total score indexed degree of change. Dichotomized at a total score less than or equal to 10, which corresponds to clinical remission, the CY-BOCS was the primary measure of responder status.

As described in detail elsewhere,[12] independent evaluators were trained to a reliable standard on the ADIS-C and the CY-BOCS through joint interviews, videotape reviews, and discussion. Reliability was maintained using within-site and trial-wide supervision, including review of videotaped interviews. Reliability at baseline for the CY-BOCS ($r = 0.81$, $P = .001$) and ascertainment of OCD on the ADIS-C ($\kappa = 0.875$, $P = .001$) were within the acceptable range.

Medication-related adverse events were inventoried using an adverse-effect checklist administered in both self-report (in the waiting room to child and parent) and clinician-interview fashion. Adverse events causing premature termination from the protocol and serious adverse events, including suicidality, were monitored by clinician report.

Statistical Methods

With the Duke University site as the data center for the trial, data entry and verification, data transfer, confidentiality and security, backup and storage, and initial data analyses were conducted under the direction of the principal investigators and the POTS statistical consultant. All analyses were conducted using an intent-to-treat model in which all assessment points at all visits were obtained insofar as possible and all available data were included in the analysis. Because the Brown University site operated under subcontract to the Penn site and enrolled a relatively small number of patients, data from the Brown and Penn sites were combined for most analyses.

Statistical analyses on the primary scalar outcome measure (CY-BOCS total score) were conducted using linear mixed-effects random regression.[23,24] Specifically, the impact of treatment on outcome at week 12 was modeled as a linear function of fixed effects for treatment, site, days since baseline (linear time

trend), and all 2- and 3-way interactions. Clinical remission (CY-BOCS score ≤ 10) was analyzed using an omnibus 4×2 χ^2 test, followed by 2×2 pairwise contrasts of condition by response us- ing the Fisher exact test for all possible combinations. For responder data only, missing data were imputed using last observation carried forward (LOCF). Confidence intervals for percentages of re- sponders were calculated using the Wald correction. In addition, to test for site differences within any treatment condition, a response by site stratified by condition analysis was run using the Mantel-Haenszel test of conditional independence. All analyses were performed using SAS version 6.12 (SAS Institute Inc, Cary, NC).

For hypotheses stipulated in the statistical plan for the 2 primary outcomes, the nominal significance level was set a priori at a 2-tailed type I error rate of .05. Under these assumptions and using pilot data on the primary scalar outcome variable obtained from prior studies,[2,9] power established prior to study initiation was greater than 99% for the omnibus test of the main effect of treatment and greater than or equal to 80% for any pairwise post hoc contrast.

To evaluate the clinical significance of the impact of treatment on outcome and to explicate site effects, effect sizes (mean standardized difference expressed as Hedge g) were calculated as $M_E - M_C/SD_{pooled}$, where M_E represents the LOCF mean of experimental treatment, M_C represents the LOCF mean of the comparison treatment, and SD_{pooled} represents pooling of the SDs from within both groups.[25] The number needed to treat—defined as the number of patients who need to be treated in order to bring about 1 additional good outcome—was calculated according to methods outlined by Sackett et al.[26]

RESULTS
Patient Disposition and Characteristics

One hundred fifty-four patients were assessed at an in-person visit for all inclusion and exclusion criteria (**FIGURE 1**). Of these, 112 patients (28 per treatment group) were randomly assigned to treatment, 60 at Duke University, 44 at Penn, and 8 at Brown University. The remaining 42 study candidates were either deemed ineligible or were not interested in participating in the study.

As indicated in Figure 1, 97 of 112 patients (87%) completed the full 12

Figure 1. Flow Diagram of a Trial of Treatments for Children and Adolescents With a Diagnosis of Obsessive-Compulsive Disorder
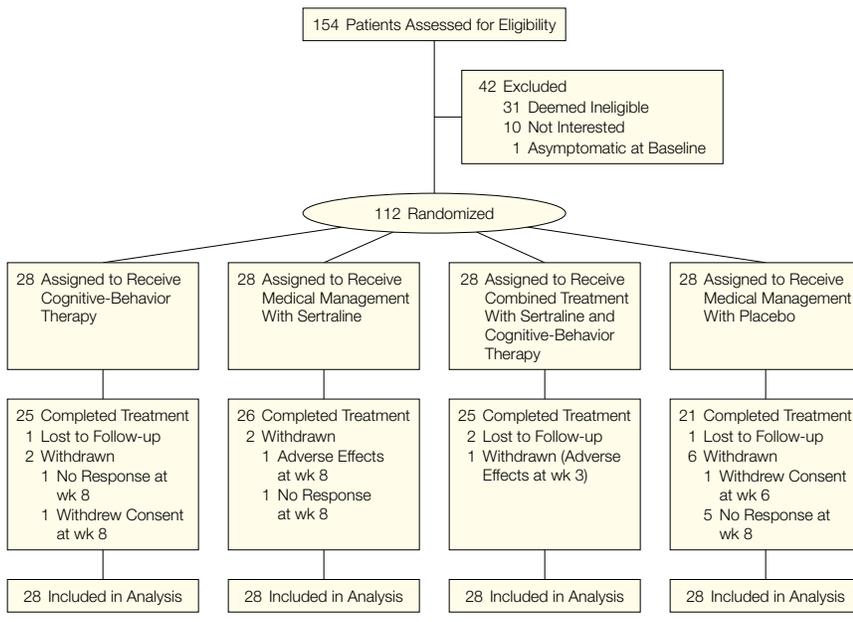
Table 1. Baseline Demographic and Clinical Characteristics by Treatment Group*

Characteristics	Cognitive-Behavior Therapy (n = 28)	Sertraline (n = 28)	Combined Treatment (n = 28)	Placebo (n = 28)
Sex, No. (%)				
Male	14 (50.0)	17 (60.7)	11 (39.3)	14 (50.0)
Female	14 (50.0)	11 (39.3)	17 (60.7)	14 (50.0)
Age, mean (SD), y	11.4 (2.8)	11.7 (2.4)	11.7 (2.8)	12.3 (3.0)
Scalar variables, mean (SD)				
CY-BOCS score†				
Obsessions	12.6 (2.6)	11.5 (2.6)	11.2 (1.8)	11.9 (2.1)
Compulsions	13.4 (2.5)	12.0 (2.6)	12.6 (1.7)	13.3 (1.7)
Total	26.0 (4.7)	22.5 (4.7)	23.8 (3.0)	25.2 (3.3)
NIMH Global Severity score‡	9.4 (1.5)	8.8 (1.5)	8.8 (1.1)	9.0 (1.2)
CGI Scale severity score§	4.9 (0.8)	4.4 (0.8)	4.6 (0.6)	4.7 (0.6)
Psychiatric comorbid disorders, No. (%)				
Internalizing‖	22 (81.5)	17 (63.0)	15 (53.6)	16 (61.5)
Externalizing¶	9 (33.3)	9 (33.3)	4 (14.3)	7 (26.9)
Tic	3 (11.1)	5 (18.5)	4 (14.3)	5 (19.2)

Abbreviations: CGI, Clinical Global Impression; CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; NIMH, National Institute of Mental Health.
*No significant pretreatment differences were found for any of these variables.
†Possible range, 0-40.
‡Possible range, 1-15.
§Possible range, 1-7.
‖Affective or anxiety disorders.
¶Attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder.

weeks of treatment, with the majority receiving the treatment as intended. Three patients receiving CBT alone, 2 receiving sertraline alone, 3 receiving combined treatment, and 7 receiving placebo did not complete treatment in their assigned groups. Of these, 4 were lost to follow-up, 2 (1 of whom moved out of the area) withdrew consent, and 2 (1 in the sertraline-alone group and 1 in the combined-treatment group) discontinued treatment with sertraline due to adverse effects. The remainder were withdrawn from treatment or received an additional out-of-protocol treatment due to lack of efficacy after a minimum of 8 weeks in their assigned treatment groups. All 112 patients were analyzed in the treatment groups to which they were assigned.

The mean (median) numbers of completed CBT sessions (out of a possible 14 sessions) in the CBT alone and the combined-treatment groups were 12 (13) and 14 (14), respectively. The mean (SD) highest daily dose of medication in the combined-treatment group was 133 (64) mg; for the sertraline-alone group the dose was 170 (33) mg, and for placebo equivalents it was 176 (40) mg. The corresponding median doses for combination treatment, sertraline alone, and placebo were 150, 200, and 200 mg, respectively.

The POTS sample is representative of youth with OCD seen in general clinical practice.[27] As indicated by a mean (SD) CY-BOCS score of 24.6 (4.1), an NIMH Global Severity score of 9.0 (1.3), and a Clinical Global Impressions Scale severity score of 4.8 (0.72), POTS patients on average fell within the moderate to moderately severe range of illness. The mean (SD) age was 11.7 (2.7) years (range, 7-17 years). The sample was evenly split between male and female patients. Forty-six percent of patients were children (aged 11 years or younger) and 54% were adolescents (aged 12 years or older). As ascertained by patient report, 92% of the sample was white, 4% African American, 3% Hispanic, and 1% Asian. As indicated by a mean (SD) scaled score of 12.0 (3.2) on the Wechsler Intelli-

Table 2. Mean CYBOCS Score, by Treatment Group and Week (n = 28)

	CY-BOCS Score, Unadjusted Mean (SD)*			
Week	Cognitive-Behavior Therapy	Sertraline	Combined Treatment	Placebo
Baseline	26 (4.6)	23.5 (4.7)	23.8 (3.0)	25.2 (3.3)
4	20.6 (6.5)	18.5 (7.5)	18.1 (6.8)	22.4 (5.4)
8	18.1 (7.9)	16.9 (8.2)	14.4 (8.1)	22.5 (4.4)
12	14.0 (9.5)	16.5 (9.1)	11.2 (8.6)	21.5 (5.4)

Abbreviation: CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale.
*Last observation carried forward used to impute missing values.

gence Scale for Children vocabulary subtest and of 10.6 (3.9) on the block design subtest, patients had slightly better verbal than nonverbal reasoning abilities ($P = .002$), while being of average intelligence.

Eighty percent of the POTS sample had at least 1 psychiatric comorbid disorder. Sixty-three percent had 1 or more internalizing (affective or anxiety) disorders; 27% had an externalizing disorder (ADHD, oppositional defiant disorder, or conduct disorder); and 16% had a comorbid tic disorder. Ten percent of the sample was taking a psychostimulant for ADHD. No patients were required to discontinue medication to enter the study. No statistically significant differences between the 4 treatment groups or between the sites were noted at baseline for these variables (**TABLE 1**).

Primary Outcomes

The mean (SD) CY-BOCS scores using LOCF are presented by treatment group in **TABLE 2**; mean (SE) CY-BOCS scores adjusted for other variables in the model are plotted by treatment group in **FIGURE 2**.

Random-coefficient regression analyses of longitudinal CY-BOCS score identified a statistically significant linear trend with time ($F_{1,289} = 239.4$, $P < .001$) as well as a time × treatment interaction ($F_{3,289} = 7.95$, $P < .001$). The overall effect of site was nonsignificant ($F_{1,104} = 0.18$, $P = .67$); however, a statistically significant site × time × treatment interaction ($F_{3,289} = 2.84$, $P = .04$) emerged. As shown in Figure 2, planned post hoc pairwise contrasts at week 12 produced a statistically significant ordering of outcomes. Specifically, combined treat-

Figure 2. Weekly Adjusted Intent-to-Treat CY-BOCS Score, by Treatment Group
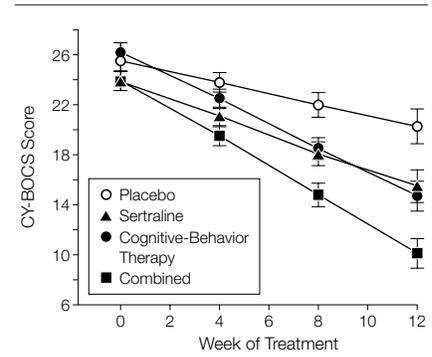
Range of possible scores for the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) is 0-40. Error bars indicate SE. Mean (SE) scores adjusted for fixed effects for treatment, site, days since baseline (linear time trend), and all 2- and 3-way interactions.

ment proved superior to CBT ($P = .008$), to sertraline ($P = .006$), and to placebo ($P < .001$). CBT alone and sertraline did not differ ($P = .80$); both CBT alone ($P = .003$) and sertraline ($P = .007$) proved statistically superior to placebo.

Using a CY-BOCS total score dichotomized at less than or equal to 10 as indicating clinical remission, the omnibus test was significant ($\chi^2_3 = 19.0$, $P < .001$). Planned pairwise contrasts for rates of clinical remission revealed that combined treatment (53.6%; 95% confidence interval [CI], 36%-70%) did not differ from CBT alone (39.3%; 95% CI, 24%-58%) ($P = .42$ by Fisher exact test) but did differ from sertraline (21.4%; 95% CI, 10%-40%) ($P = .03$ by Fisher exact test) and from placebo (3.6%; 95% CI, 0%-19%) ($P < .001$ by Fisher exact test). Use of CBT alone did not differ from sertraline ($P = .24$) but did differ from placebo ($P = .002$). Sertraline did not differ from placebo ($P = .10$). Test for the effect

Table 3. Treatment-Emergent Adverse Events in Medication-Treated Patients*

	No. (%)		
Adverse Event	Sertraline (n = 28)	Combined Treatment (n = 28)	Placebo (n = 28)
Decreased appetite	5 (18)	4 (14)	0
Diarrhea	6 (21)	0	1 (4)
Enuresis	2 (7)	2 (7)	0
Motor overactivity	1 (4)	6 (21)	1 (4)
Nausea	7 (25)	5 (18)	1 (4)
Stomachache	8 (29)	4 (14)	2 (7)

*Data are for events occurring in at least 5% of sertraline-treated patients and with an incidence of at least 2 times that seen in placebo-treated patients in either the sertraline-alone or the combined-treatment group. Medication-related adverse events were not recorded for patients treated with cognitive-behavior therapy alone.

of site proved nonsignificant (Mantel-Haenszel $\chi^2_1 = 0.006$, $P = .94$). Thus, the pattern of clinical remission revealed the same ordering of treatment effects as in the random-regression analysis of the CY-BOCS scores, with slight differences in statistical significance in comparing the treatment groups.

The clinical significance (magnitude) of the impact of treatment on outcome was evaluated by calculating effect sizes (expressed as Hedge g) relative to placebo for the scalar CY-BOCS and number needed to treat for the CY-BOCS dichotomized by clinical remission. Effect sizes for combined treatment, CBT alone, and sertraline were 1.4, 0.97, and 0.67, respectively. Echoing the effect-size analysis, the numbers needed to treat for combined treatment, CBT alone, and sertraline relative to placebo were 2 (95% CI, 2-3), 3 (95% CI, 2-4), and 6 (95% CI, 4-11), respectively.

Additional contrasts and effect-size calculations for the Penn and Duke sites only (Brown site data were excluded from this subanalysis because of small cell sizes) were performed to explicate the statistically significant site × time × treatment interaction observed in the random-regression analyses. Sertraline alone at the Duke site proved superior to sertraline alone at the Penn site ($P = .02$), whereas CBT alone at Penn was superior to CBT alone at Duke ($P = .05$); there were no statistically significant site differences for combined treatment or placebo. At the Penn site, very large effects relative to placebo were observed for CBT alone (effect size, 1.6) and for

combined treatment (effect size, 1.5), whereas sertraline yielded a moderate effect size (0.53). At the Duke site, CBT alone yielded a moderate effect size (0.51), whereas combined treatment and sertraline yielded large effect sizes (1.29 and 0.8, respectively), suggesting that combined treatment is less susceptible to setting-specific variations in treatment outcome.

Safety and Tolerability

As indicated by the fact that the great majority of patients received their treatment as intended, POTS treatments proved acceptable to patients and were generally well tolerated.

TABLE 3 reports medication-related adverse events occurring in at least 5% of patients treated with sertraline (either sertraline alone or combined treatment) and with an incidence at least 2 times that seen in patients treated with placebo. As expected, sertraline conditions experienced a numerical excess of medication-related adverse events compared with placebo. Two sertraline-treated patients experienced behavioral activation manifested as increased motor overactivity and impulsivity. Activation resolved with reduction in medication dose. An additional 5 patients treated with sertraline and 1 treated with placebo experienced mild increases in motor overactivity without impairment in impulse control. There were no episodes of mania, hypomania, or depression, and no serious adverse events occurred during the course of the study. Importantly, no patient became suicidal or made a suicide attempt.

COMMENT

Focused on the initial treatment of OCD in children and adolescents, the POTS was designed to answer clinically important questions concerning (1) the benefit(s) of combined treatment relative to medication management with an SSRI or to CBT alone and (2) the benefit(s) of CBT and medication relative to placebo. The outcome is clear and the clinical implications straightforward. Patients treated with CBT either alone or in combination with medication showed a substantially higher probability of improvement, with the edge going to combination treatment over CBT alone in one site but not in the other. Sertraline alone proved statistically superior to placebo, confirming the efficacy of medication used to treat OCD in youth; however, the effect size of CBT alone (0.97) was larger than that for sertraline alone (0.67), and more patients receiving CBT alone entered remission than did those receiving sertraline alone (39.3% vs 21.4%, respectively), though these differences did not reach statistical significance. Thus, we conclude that children and adolescents with OCD should begin treatment with CBT alone or with CBT plus an SSRI.

While retaining many efficacy elements, the sampling frame for the POTS was designed to recruit a broadly representative sample of youth with OCD. Given the tendency of industry-funded registration trials to exclude patients with comorbid conditions typical of those seen in clinical practice, it is especially noteworthy that 63% of the POTS sample exhibited a comorbid internalizing disorder and 26% a comorbid externalizing disorder. Furthermore, despite a somewhat more comorbid population, the effect size reported for sertraline relative to placebo is comparable to that in our previous study of sertraline in pediatric OCD[4] and to other published studies of medication in pediatric OCD,[6] lending confidence to the overall estimates of the clinical impact of treatment. Accordingly, we conclude that results of the study should be broadly appli-

cable to youth with OCD seen in clinical practice.

Duke University and the University of Pennsylvania are noted for their expertise in the use of CBT for pediatric OCD. Despite a prestudy assumption that equivalent expertise would translate to equivalent outcomes, we identified a statistically significant site × treatment interaction that indicates that the impact of CBT without concurrent medication was greater at the Penn site than at the Duke site, whereas no site effect was found for the combined treatment. Although this study used procedures designed to maximize protocol adherence, including direct supervision, case conferences, training meetings, and tape review,[12] these results nonetheless may have arisen due to a site or a therapist effect (associated with alliance, competence, or protocol adherence), or perhaps to patient characteristics that may differ across therapists even though there were no apparent baseline differences in patient characteristics between the Penn and Duke sites. Because these variables vary in vivo, the presence of site differences can be thought to contribute to the generalizability of the overall result; eg, the overall outcome favoring CBT either alone or in combination with an SSRI cannot simply be the result of choosing sites with CBT expertise. Additionally, the strength of CBT alone at the Penn site contributed to our recommendation that CBT alone be a first-line option as initial treatment. Lastly, the finding that the sites did not differ in the impact of combined treatment suggests that when the results of CBT are attenuated for some reason, the addition of medication is important.

Future papers will examine predictors of treatment response as well as diverse behavioral/symptomatic and function outcomes and will thereby begin to address the question of most interest to clinical decision-makers, namely, which treatment should be used for which child with which set of clinical characteristics.[28]

Adverse events—particularly induction of mania and, as a matter of recent debate, suicidality—are an important concern in children and adolescents treated with SSRIs.[29] Some meta-analyses of published and unpublished studies of antidepressants in pediatric major depressive disorder suggest that the overall risk-to-benefit ratio may be unfavorable, except for fluoxetine.[30] As a result, regulators in the United Kingdom and the United States have issued advisories regarding the use of SSRIs in the pediatric population. While the advisories appropriately call for careful monitoring of potential adverse outcomes in youth treated with antidepressant medication, SSRI treatment of pediatric OCD generally is thought to show a favorable risk-to-benefit ratio.[6] The US Food and Drug Administration is currently reviewing the adverse event profiles of all antidepressants to make a final determination regarding risk for suicidality. It is reassuring in this study (as in others[6]) that treatment was well tolerated, with no evidence of treatment-emergent harm to self or to others.

The POTS is based on a theoretical model that connects disorder (OCD), well-validated treatment components (sertraline and CBT), and outcome (reduced OCD and collateral symptoms), which ideally should make the POTS treatment manuals and procedures widely applicable in a variety of mental health settings. In particular, we believe that the results of this study will contribute to the appreciation by nonphysician mental health clinicians of the strengths and limitations of pharmacological treatments and to the appreciation by physicians of evidence-based psychosocial treatments. In turn, this may help fertilize further cross-disciplinary collaboration in pediatric mental health care.

Finally, the POTS carries significant public health implications for the management of OCD in youth and for future directions in research. Pediatric OCD is a common, chronic, and often undiagnosed psychiatric disorder that, if not adequately treated, is associated with considerable morbidity extending into adulthood. As illustrated by the fact that the overwhelming majority of POTS patients completed treatment as intended using treatment protocols intended for use by frontline clinicians, POTS treatments are both acceptable and practical in routine clinical practice. Unfortunately, despite ready availability of the CBT protocol,[20] only a small minority of children and adolescents with OCD receive state-of-the-art treatment(s) for reasons that may include features of the intervention itself as well as variables pertaining to the practitioner, client, model of service delivery, organization, and service system.[31] Clinical experience suggests that most youth with OCD receive SRI monotherapy often augmented with an atypical neuroleptic agent rather than CBT alone or combined treatment consisting of CBT and medication management. While it is not unreasonable to expect that wider availability of CBT should reduce the illness burden associated with OCD across the lifespan, barriers to transporting evidence-based treatments from specialty clinics to community practice must be successfully addressed.[32] In this context, it is imperative that the focus of research turn to identifying and testing dissemination strategies for CBT as well as to procedures for managing partial response to medication monotherapy using CBT augmentation. In this context, the POTS, which confirms and extends expert recommendations,[21,33] ideally should exert a substantial impact on evidence-based practice in the treatment of pediatric OCD.

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