Cognitive Behavior Therapy Augmentation of Pharmacotherapy in Pediatric Obsessive-Compulsive Disorder

The Pediatric OCD Treatment Study II (POTS II) Randomized Controlled Trial

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Context The extant literature on the treatment of pediatric obsessive-compulsive disorder (OCD) indicates that partial response to serotonin reuptake inhibitors (SRIs) is the norm and that augmentation with short-term OCD-specific cognitive behavior therapy (CBT) may provide additional benefit.

Objective To examine the effects of augmenting SRIs with CBT or a brief form of CBT, instructions in CBT delivered in the context of medication management.

Design, Setting, and Participants A 12-week randomized controlled trial conducted at 3 academic medical centers between 2004 and 2009, involving 124 pediatric outpatients between the ages of 7 and 17 years with OCD as a primary diagnosis and a Children's Yale-Brown Obsessive Compulsive Scale score of 16 or higher despite an adequate SRI trial.

Interventions Participants were randomly assigned to 1 of 3 treatment strategies that included 7 sessions over 12 weeks: 42 in the medication management only, 42 in the medication management plus instructions in CBT, and 42 in the medication management plus CBT; the last included 14 concurrent CBT sessions.

Main Outcome Measures Whether patients responded positively to treatment by improving their baseline obsessive-compulsive scale score by 30% or more and demonstrating a change in their continuous scores over 12 weeks.

Results The medication management plus CBT strategy was superior to the other 2 strategies on all outcome measures. In the primary intention-to-treat analysis, 68.6% (95% CI, 53.9%-83.3%) in the plus CBT group were considered responders, which was significantly better than the 34.0% (95% CI, 18.0%-50.0%) in the plus instructions in CBT group, and 30.0% (95% CI, 14.9%-45.1%) in the medication management only group. The results were similar in pairwise comparisons with the plus CBT strategy being superior to the other 2 strategies ($P < .01$ for both). The plus instructions in CBT strategy was not statistically superior to medication management only ($P = .72$). The number needed-to-treat analysis with the plus CBT vs medication management only in order to see 1 additional patient at week 12, on average, was estimated as 3; for the plus CBT vs the plus instructions in CBT strategy, the number needed to treat was also estimated as 3; for the plus instructions in CBT vs medication management only the number needed to treat was estimated as 25.

Conclusions Among patients aged 7 to 17 years with OCD and partial response to SRI use, the addition of CBT to medication management compared with medication management alone resulted in a significantly greater response rate, whereas augmentation of medication management with the addition of instructions in CBT did not.

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Obsessive-compulsive disorder (OCD) affects up to 1 in 50 people,[1] is evident across development,[2] and is associated with substantial dysfunction and psychiatric comorbidity.[3,4] Randomized controlled trial findings support the efficacy of pharmacotherapy with serotonin reuptake inhibitors (SRIs), cognitive behavior therapy (CBT) involving exposure plus response prevention, and combined treatment.[5-7] However, a paucity of expertise in pediatric OCD prevents most families from accessing exposure plus response prevention or combined treatment. Outcome data for pharmacotherapy alone, the most widely available treatment, indicate that partial response is the norm and clinically significant residual symptoms often persist even after an adequate trial.[8,9] Augmenting SRI treatment with exposure plus response prevention was found efficacious in a randomized controlled trial of adult patients with OCD,[10] but this approach has yet to be examined in youth.

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These observations led us to develop a brief protocol, instructions in CBT, for delivery in the context of medication management by child and adolescent psychiatrists. This integrated treatment (medication management plus instructions in CBT) was designed for use in clinical practice settings that impose limits on session frequency and duration; our interest in generalizing study findings to such settings informed the sampling frame and treatment protocols for this pragmatic trial. We hypothesized that a full CBT protocol plus medication maintenance would be superior to both medication management plus instructions in CBT and medication management alone and that medication management plus instructions in CBT would be superior to medication management alone.

METHODS

Design

The rationale, design considerations, assessment instrument psychometrics, and research methods for Pediatric Obsessive-Compulsive Disorder Treatment Study II (POTS II) have been described elsewhere.[11] Briefly, this 12-week randomized parallel group controlled trial included 3 sites(University of Pennsylvania, Duke University, and Brown University) and 3 treatment conditions that were measured at 4-week intervals (medication management alone, medication management plus instruction in CBT, or medication management plus CBT). Although medication management does not control for contact time, it does parallel treatment as typically delivered in community settings. The institutional review board at each site approved the protocol.

Participants

Patients were included if they were aged 7 through 17 years, had a primary OCD diagnosis according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) criteria, had clinically relevant residual OCD symptoms as defined by a score of 16 or higher on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), had been determined by a study psychiatrist to have experienced partial response to an adequate SRI trial, and were being treated as an outpatient. Patients were excluded if their primary mental health diagnosis was something other than OCD, had pervasive developmental disorder(s), did not meet study requirements for an adequate SRI trial, did not have an adequate CBT trial (>10 sessions), were pregnant, had pediatric autoimmune neuropsychiatric disorders associated with strep infection, or were taking more than 1 SRI concurrently.

Determination of Eligibility

Eligibility was assessed via a multigate procedure designed to minimize patient burden and maximize efficiency: gate A involved a brief telephone screening with the parent or guardian; gate B1 was the intake interview, which included obtaining parental informed consent and participant assent, assessment of OCD symptoms using the CY-BOCS,[12,13] and review of current medications and their effects; gate B2 involved a diagnostic evaluation using the Anxiety Disorders Interview Scale for Children[14] to survey comorbid conditions; gate C1 was the baseline assessment (week 0); and gate C2 was a separate meeting in which the outcome of randomization was revealed to the family. To establish partial response at gate B1, a study pharmacotherapist met with the family to determine whether at least some symptom reduction was evident from the current medication regimen and whether the patient was optimized on the current SRI, which was defined as at least 3 weeks of stable OCD symptoms at an SRI dose equal to the recommended upper dose, a flat dose-response curve for 1-dose increment above the minimum recommended starting dose, or reported adverse effects at a dose higher than the current dose.[11] Progression from gate A through gate C2 was typically completed within 3 weeks.

Randomization

Patients were randomly assigned to 1 of the 3 treatment conditions between September 2004 and March 2009, using a computer-generated permuted blocking procedure, stratified by site, sex, age (<12 vs ≥12 years), and baseline severity as measured with the Clinical Global Impression-Severity scale (<5 vs ≥5).

Treatments

Medication Management. All randomized patients were assigned to a child/adolescent psychiatrist from whom they received maintenance SRI medications for the duration of the study; treatment was provided according to the medication management treatment manual. Downward adjustments of SRI dosing due to medication adverse events were permitted, but medication could not be increased without a premature termination. A total of 7 in-person medication management visits were conducted over 12 weeks, each lasting approximately 35 minutes. Study pharmacotherapists treating patients in the medication management only strategy or the plus CBT group monitored clinical status and medication effects and also offered general encouragement to resist OCD. Systematic or unsystematic exposure plus response prevention, insight-oriented or interpersonal psychotherapies, other CBT interventions, or family therapies were proscribed during the 12-week study period. For each treatment group, review of taped sessions in clinical supervision and independent rating of randomly selected tapes was used to promote treatment adherence.

CBT. The CBT protocol was based on a published treatment manual of established efficacy[15] and consisted of 14 one-hour-long visits conducted over 12 weeks involving psychoeducation, cognitive training, development of treatment hierarchies to arrange feared situations from least to most anxiety-provoking to guide exposure treatment, and exposure plus response prevention. A study psychologist administered CBT augmentation in the plus CBT condition. Psychoeducation, defining OCD as the identified problem, cognitive training, and development of a treatment hierarchy took place during visits 1 through 4, exposure plus

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response prevention comprised visits 5 through 12, with the last 2 sessions incorporating generalization training and relapse prevention. 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. As in clinical practice, study psychiatrists and psychologists were aware that patients assigned to medication management plus CBT were also seeing another treating clinician.

Instructions in CBT. In the plus instructions in CBT condition, the pharmacotherapist assigned to manage medication also provided instruction in CBT procedures. The instructions in CBT were administered according to protocol (7 visits over 12 weeks), with an average time of 45 minutes. The additional psychiatrist time beyond medication management was used to introduce CBT principles and provide time to plan implementation of these skills between sessions. Specifically, instructions in CBT included psychoeducation, establishing and reevaluating a simple stimulus hierarchy, identifying exposure plus response prevention targets, and assigning homework; 2 brief telephone check-ins were prescribed during treatment to provide guidance of CBT implementation at home. Instructions in CBT did not include therapist-assisted exposure; imaginal exposure; and didactic parent sessions, which was necessitated by our interest in testing a protocol that could be feasibly implemented by psychiatrists in clinical practice settings that do not typically allow for long sessions.

Supervision and Oversight

Each site had major supervisory responsibilities: University of Pennsylvania provided clinical supervision of CBT and instructions in CBT; Duke University organized data management and statistical analyses; and Brown University provided clinical supervision of all medication management. Academic psychiatrists and psychiatry residents with a range of experience in pediatric psychopharmacology provided for medication management treatment and instructions in CBT; these clinicians had been exposed to CBT as part of their work on the sites' clinical teams yet were not specifically expert in CBT with pediatric OCD. Psychologists and psychology trainees who provided CBT in the plus CBT condition also had a range of general clinical experience but had been trained specifically in delivering CBT for pediatric OCD as part of their work with the respective sites' clinical teams. Pharmacotherapists treating cases in the plus instructions in CBT condition participated in separate site-specific and cross-site supervision meetings for both medication management only and plus instructions in CBT; CBT therapists received separate site-specific and cross-site supervision. An independent data and safety monitoring board provided regular oversight and met biannually during the study and upon its completion.

Measures

The *DSM–IV* diagnoses of OCD and comorbid psychiatric conditions were ascertained using the research diagnostic version of the Anxiety Disorders Interview Scale for Children, an established measure with acceptable psychometric properties.[14,16] Obsessive-compulsive disorder symptom severity was measured using the CY-BOCS, an interviewer-rated instrument that assesses obsessions and compulsions separately on time consumed, distress, interference, resistance, and control; it yields separate severity scores for obsessions and compulsions (0-20) and a composite severity score (0-40).[12,13] Consistent with signal detection analyses examining the optimal criterion for treatment response,[17] a CY-BOCS score reduction of 30% or more from baseline to week 12 was used as the criterion for determining patient response and was the primary dichotomous outcome measure. Secondary, continuous outcome measures of OCD symptom severity, the CY-BOCS and the National Institute of Mental Health–(NIMH-GOCS) Global Obsessive Compulsive Scale, were also examined at week 12. Demographic (eg, sex, age, race, and ethnicity, as required by NIMH) and medical history data were collected using the Conners/March Developmental questionnaire,[18] a self-report instrument completed by the child's parent(s). Global symptom severity was measured using the Clinical Global Impression-Severity Scale,[19] ranging from 1 (not ill) to 7 (extremely ill).

Because of the nature of the experimental design, families and clinicians were aware of the condition assignment; consequently, blinding for the outcome measures was maintained by use of a trained independent evaluator not otherwise involved in the study. Independent evaluators were trained to a reliable standard via joint interviews, reviews of videotaped interviews, and discussion. Reliability was maintained via within- and cross-site supervision that included monthly reviews and re-ratings of videotaped interviews. Approximately 10% of CY-BOCS sessions were randomly selected and then coded by all independent evaluators. Variability among coders was discussed on the call to help stem rater drift. Interrater reliability during the trial remained high using the independent evaluator–supervisor CY-BOCS rating as the gold standard (intraclass correlation = 0.97).

Documentation and Clinical Management of Adverse Events

Because participants took an active SRI throughout the trial, adverse events were assessed at each psychiatric treatment visit using the Pediatric Adverse Event Rating Scale.[20]

Sample Size and Power

Assuming response rates of 70% for the plus CBT condition, 40% for the plus instructions in CBT condition, and 10% for the medication management only condition, a 5% type I error, 2-tailed χ^2 test, and a planned total sample size of 150 (50 per group), the study was designed to detect a difference in the 3 response rates, the primary outcome, with 99% probability. Recruitment issues likely related to the US Food and Drug Administration's black box warning about the use of SRIs in youth (October 2004) were

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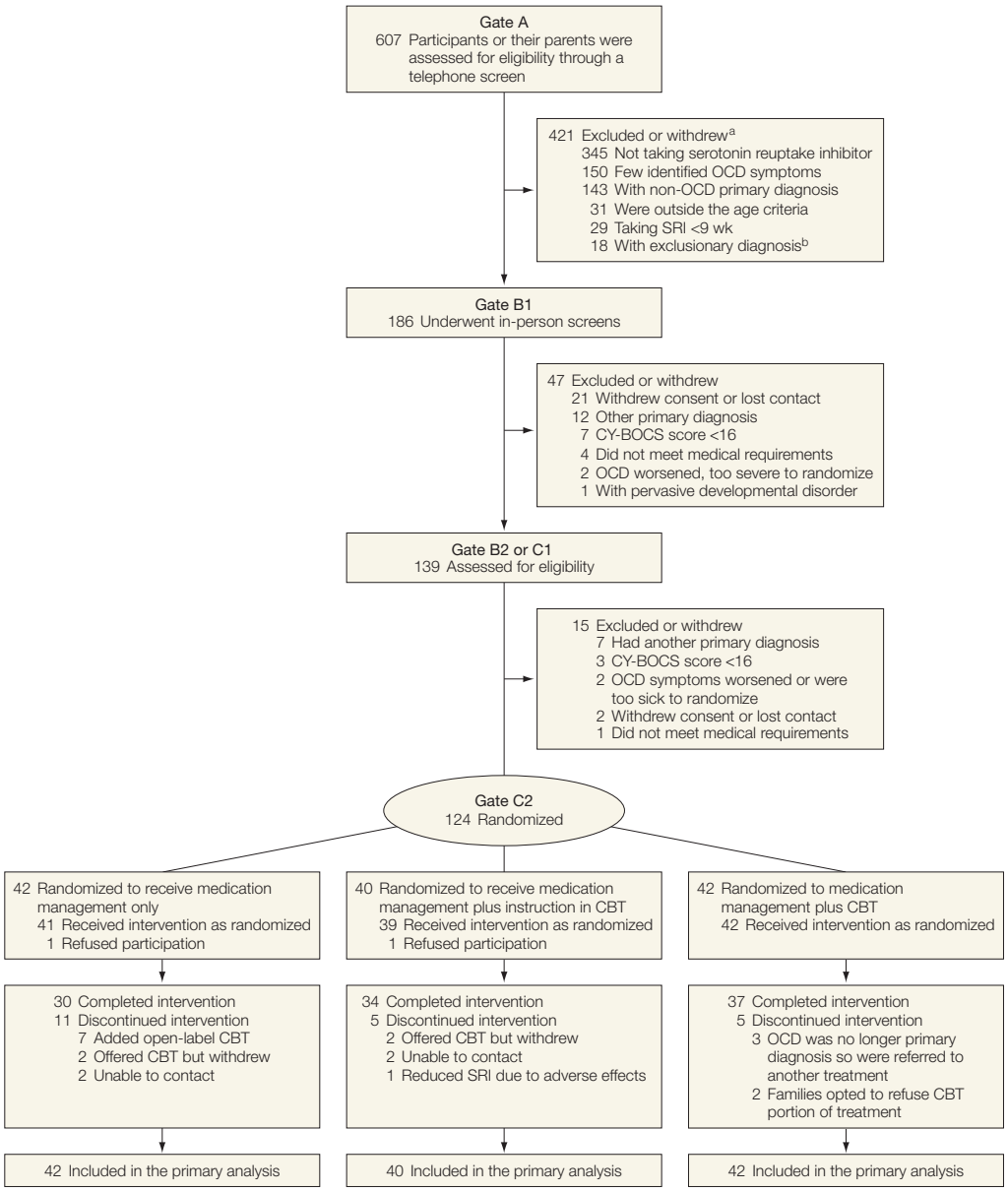
encountered early on in the study, thus limiting the final sample size to 124 randomized participants.

Missing Data

As part of the study design, efforts were made to collect all outcomes on all randomized participants even when treatment was prematurely terminated.[11] Prior to analysis, we used multiple imputation to replace missing values.[21] A sequential regression multivariate imputation algorithm[22] was used, as implemented in the IVEware package for SAS.[23] The imputation model included all longitudinal outcome measures, time since randomization, treatment indicators, putative moderators and mediators,[11] and the 4 stratification variables described above. Five data sets were generated. Results reported below were calculated using Rubin rules[22] for combining the results of identical analyses performed on each of the 5 imputed data sets.

Figure 1. Flow of Participants Through the Trial



[a] Gate A exclusions are more than 421 because some patients had more than 1 reason for their exclusion.
[b] Of these, 13 had diagnosis of pervasive developmental disorder or mental retardation; 5 had pediatric autoimmune neruropsychiatric disorders associated with streptococcal infections. CBT indicates cognitive behavior theratpy; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; OCD; obsessive-compulsive disorder; SRI, serotonin reuptake inhibitor.

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Statistical Analysis

All randomized participants were included in the analyses in accordance with intention-to-treat (ITT) principles. A multivariate χ^2 test was used to test for between-group differences in response rates at week 12. Group-specific response rates and planned pair-wise differences in the response rates were also calculated. Separate longitudinal regression models were used to examine mean differences in the 2 continuous outcomes (CY-BOCS, NIMH-GOCS) between the 3 randomized treatment groups at each assessment visit. Each regression model included indicators of time (assessment visit), group assignment, and all time × group interaction terms. Baseline stratification variables used in the randomization procedure (site, sex, age, and baseline severity) were also included in each model a priori. Residual error terms were assumed to follow a mean-0, normal distribution with an unstructured covariance structure used to capture the within-person correlation over time. The fitted models were used to report mean scores at each assessment visit and make inferences about between-groups comparisons at the final assessment visit. Tests were 2-sided, and $P < .05$ was considered statistically significant. The sequential Dunnett test was used to control the overall (family-wise) error rate.[24] Longitudinal models were fit using PROC MIXED in SAS Statistical Software, version 9.2 Level 2M2 (SAS Institute Inc, Cary, North Carolina). Throughout the analyses, adjusted degrees of freedom were implemented and presented[25] using the empirical distribution function option in SAS. When conducting analyses based on imputed data sets, χ^2 test results are combined and reported commonly as an F statistic. In our case, we used the SAS macro COMBCHI.[26]

To enhance interpretation of the results for response, we calculated the number needed to treat[21] with medication management plus CBT and plus instructions in CBT relative to medication management alone. For the continuous outcomes, we calculated standardized between-group mean differences[27] at the week 12 visit.

Table 1. Baseline Characteristics and Observed Cases by Time point

Variable	No. (%) of Participants: Medication Management: Only (n = 42)	+ Instructions in CBT (n = 40)	+ CBT (n = 42)	All Participants (n = 124)	P Value[a]
Study center					
Brown University	18 (42.9)	15 (30.2)	15 (35.7)	48 (38.7)	.90
Duke University Medical Center	10 (23.8)	11 (27.5)	14 (35)	35 (28.2)	
University of Pennsylvania	14 (33.3)	14 (35)	13 (32.5)	41 (33.1)	
Age, mean (SD), y	14.34 (2.51)	13.76 (2.72)	12.71 (2.88)	13.60 (2.77)	.02
7-11 y	10 (23.8)	12 (30.0)	18 (42.9)	40 (32.3)	.16
Girls	22 (52.4)	21 (52.5)	23 (54.8)	66 (53.2)	.97
Race					
White	38 (90.5)	38 (95)	39 (92.9)	115 (92.7)	.66
Black	1 (2.4)	1 (2.5)	1 (2.4)	3 (2.4)	
Asian	2 (4.8)	0	0	2 (1.6)	
Mixed	0	0	1 (2.4)	1 (0.8)	
Not reported	1 (2.4)	1 (2.5)	1 (2.4)	3 (2.4)	
Ethnicity					
Not Hispanic or Latino	41 (97.6)	39 (97.5)	39 (92.9)	119 (96.0)	.14
Hispanic or Latino	0	0	2 (4.8)	2 (1.6)	
Not reported	1 (2.4)	1 (2.5)	1 (2.4)	3 (2.4)	
OCD baseline severity					
CY-BOCS, mean (SD)	26.08 (5.12)	27.40 (4.75)	25.45 (5.18)	26.29 (5.05)	.21
NIMH-GOCS, mean (SD)	9.60 (1.77)	9.95 (1.81)	9.31 (1.75)	9.61 (1.78)	.27
Clinical Global Impression Severity score					
Mean (SD)	4.88 (0.15)	5.10 (0.81)	4.81 (0.14)	4.93 (0.90)	.32
<5	13 (30.9)	10 (25)	17 (40.5)	40 (32.3)	
≥5	29 (69)	30 (75)	25 (59.5)	84 (67.7)	
Baseline comorbidities					
Any	27 (64.3)	26 (65)	21 (50)	74 (59.7)	.29
ADHD	11 (26.2)	9 (22.5)	7 (16.7)	27 (21.8)	.57
Anxiety/mood	20 (47.6)	18 (45)	17 (40.5)	55 (44.4)	.80
Tic disorder	9 (21.4)	8 (20)	2 (4.8)	19 (15.3)	.06
Externalizing	1 (2.4)	1 (2.5)	0	2 (1.6)	.59
Observed cases					
Baseline	42	40	42	124	
Week					
4	38	37	39	114	
8	36	35	38	109	
12	37	34	39	110	
Current SRIs					
Citalopram	4 (9.5)	5 (12.5)	4 (9.5)	13 (10.5)	.39
Fluoxetine	16 (38.1)	9 (22.5)	10 (23.8)	35 (28.2)	
Fluvoxamine	6 (14.3)	8 (20.0)	8 (19.0)	22 (17.7)	
Paroxetine	2 (4.8)	4 (10.0)	1 (2.4)	7 (5.6)	
Sertraline	13 (31.0)	13 (32.5)	14 (33.3)	40 (32.2)	
Other	1 (2.4)	1 (2.5)	5 (11.9)	7 (5.6)	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CBT, cognitive behavior therapy; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; NIMH-GOCS, National Institute of Mental Health Global Obsessive Compulsive Scale; OCD, obsessive-compulsive disorder; SRI, serotonin reuptake inhibitor

[a] *P* values for continuous variables were generated from 1-way analysis of variance; *P* values for categorical variables were generated from Pearson χ^2.

RESULTS

Recruitment and Retention

The consort diagram is depicted in detail in FIGURE 1. Participants were re-

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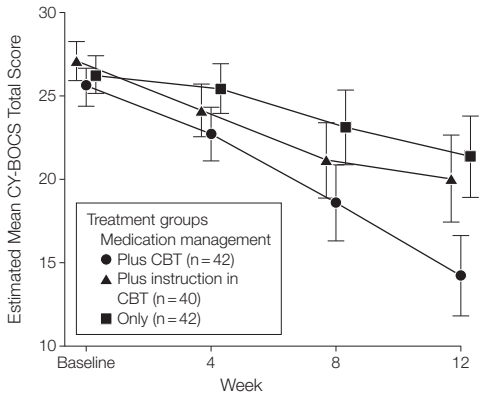
cruited from site clinics; schools; primary care physicians; mental health professionals; and paid and public service advertisements in local media, including newspapers, radio, Internet, and television. Of the 124 participants who underwent randomization, 118 (95.2%) completed at least 1 postbaseline assessment. The mean number of completed CBT sessions in the plus CBT condition was 12.50 (CI 95%, 11.38-13.62) out of a possible 14 sessions; for plus instructions in CBT, the mean number of completed sessions was 6.0 (CI 95%, 5.43-6.66), and for medication management only, the mean was 6.48 (CI 95%, 6.02-6.93) out of a possible 7 sessions. A total of 101 participants (81.5%) completed acute treatment. Among those who did not complete acute treatment, 13 dropped out before posttest: 2 refused at randomization and were lost to follow-up (medication management only, 1; plus instructions in CBT, 1), 4 received some treatment as randomized but subsequently dropped out of the study and were lost to follow-up (medication management only, 2; plus instructions in CBT, 2), and 7 were prematurely terminated due to worsening symptoms and dropped instead of receiving ancillary treatment (medication management, 2; plus instructions in CBT, 2; plus CBT, 3). The other 10 participants who had terminated prematurely because they had received out-of-protocol treatment remained in the study for outcome assessments (medication management only, 7; plus instructions in CBT, 1; plus CBT, 2). Investigation of postrandomization activity indicated that patients in the medication management–only group were more likely to prematurely terminate and receive out-of-protocol treatment (χ^2_2, 6.40; $P<.04$).

Figure 2. Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) Scores During 12 Weeks of Acute Treatment



Points are group-specific estimated mean CY-BOCS scores at each time point. Point estimates were derived from the fitted linear mixed models, averaged over site, sex, age (<12 vs ≥12 years), and baseline severity (Clinical Global Impression Severity scale, <5 vs ≥5). Error bars are point-wise 95% CIs.

Sample Characteristics

TABLE 1 summarizes baseline clinical characteristics and SRI medication regimens of the randomized sample by treatment group. When treated as a categorical covariate (<12 vs ≥12) as prespecified in the stratified randomization scheme, age did not differ by treatment groups ($P=.16$). However, when treated as a continuous variable, age was found to be significantly different between groups ($P=.02$), with younger children more likely to be in the CBT plus medication management group than in the medication management–only group. No other significant differences were identified. All patients were currently taking an SRI, which they had been taking for an average of 74.9 weeks (SD, 73.2; range, 9-402 weeks) prior to study entry. For 51% of the sample, the current medication was their first SRI trial; 29% had 1 other past SRI trial, 8.9% had 2, 6.5% had 3, 2.4% had 4, and 1.6% had 5. Some concomitant medications for comorbid psychiatric or medical conditions were also permitted, the most common of which were stimulant medications for attention-deficit/hyperactivity disorder (13.7%).

ITT Analysis

In the primary ITT analysis, the percentages of participants at 12 weeks who had at least a 30% reduction in their CY-BOCS baseline score were 68.6% in the plus CBT group (95% CI, 53.9%-83.3%), 34.0% in the plus instructions in CBT group (95% CI, 18.0%-50.0%), and 30.0% in medication management only–group (95% CI, 14.9%-45.1%). The multivariate χ^2 test indicated a significant difference between groups (χ^2_2, 136.57 = 6.44, $P=.002$). Planned pairwise comparisons show that the plus CBT condition was superior to both the medication management only–condition ($t_{100.66}=3.43$, $P<.001$) and the plus instructions in CBT condition ($t_{373.62}=3.16$, $P=.002$). The plus instructions in CBT condition was not statistically better than medication management–only condition ($t_{140.76}=0.35$, $P=.72$). Planned pairwise comparisons of the continuous week-12 outcomes were comparable with the findings for response among those in the plus CBT condition being superior to both the medication management–only ($t_{189.48}=4.00$, $P<.001$) and the plus instructions in CBT conditions ($t_{219.05}=3.26$, $P=.001$); however, the plus instructions in CBT and medication management–only conditions were not significantly different from each other ($t_{390.39}=0.75$, $P=.45$; FIGURE 2). For the NIMH-GOCS, the plus CBT condition was superior to both medication management–only ($t_{208.58}=4.37$, $P<.001$) and the plus instructions in CBT conditions ($t_{246.42}=3.29$, $P=.001$); however, the plus instructions in CBT

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and medication management–only conditions were not significantly different from each other ($t_{437.06}$=1.11, P=.27). An additional sensititivity analysis showed that the results did not differ when adjusted for continuous age differences. TABLE 2 provides a detailed description of point estimates, planned comparisons, and the respective effect sizes for each continuous variable.[26]

A multivariate χ^2 test found no statistically significant site × treatment interactions for response at the 12-week visit (P=.28). Similarly, no sites × site treatment interactions were found at the week-12 visit for the continuous outcomes: CY-BOCS (P=.15) or NIMH-GOCS (P=.72).

Effect Estimates of Clinical Significance

Treatment effect sizes for week-12 CY-BOCS scores were 0.85 (95% CI, 0.43-1.27) for the plus CBT vs medication management only, and 0.16 for the plus instructions in CBT vs medication management only; these correspond to large and small treatment effect sizes, respectively. The number needed to treat with the plus CBT vs medication management–only groups to see 1 additional response at week 12, on average, was estimated as 3; for the plus CBT vs plus instructions in CBT groups, the number needed to treat was also estimated as 3; for the plus instructions in CBT vs medication management–only groups, the number needed to treat was estimated as 25.

Table 2. Group-Specific Response Rates at Week 12

Week 12 Variable	Rate or Mean (95% CI)		
	Responder Status[a]	CY-BOCS[b]	NIMH-GOCS[c]
Estimated means[d]			
Medication management			
+ CBT	0.69 (0.54 to 0.83)	14.23 (11.85 to 16.62)	5.59 (4.82 to 6.36)
+ Instructions in CBT	0.34 (0.18 to 0.50)	20.05 (17.45 to 22.65)	7.47 (6.65 to 8.30)
Only	0.30 (0.15 to 0.45)	21.35 (18.89 to 23.80)	8.08 (7.29 to 8.89)
Effect sizes[e]			
Medication management			
+ CBT vs medication management only	0.39 (0.16 to 0.61)	0.85 (0.43 to 1.27)	0.93 (0.51 to 1.35)
+ CBT vs + instructions in CBT	0.35 (0.13 to 0.56)	0.70 (0.28 to 1.12)	0.70 (0.28 to 1.12)
+ Instructions in CBT vs medication management only	0.04 (–0.18 to 0.26)	0.16 (–0.25 to 0.56)	0.23 (–0.18 to 0.63)

Abbreviations: CBT, cognitive behavior therapy; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; NIMH-GOCS, National Institute of Mental Health–Global Obsessive Compulsive Scale
[a] Responder status scores range from 0.0 to 1.00 reflecting the proportion of responders.
[b] CY-BOCS scores range from 0 to 40 with larger scores reflecting more OCD symptoms.
[c] NIMH-GOCS scores range from 1 to 15 with larger scores reflecting more OCD symptoms.
[d] For responder status: the estimated rate of response (30% reduction of CY-BOCS from baseline) at week 12. For CY-BOCS, NIMH, and CGI-S estimated mean score at week 12 from the fitted linear mixed models, averaged over site, sex, age (<12 vs ≥12 years), and baseline severity (CGI-S, <5 vs ≥5).
[e] For responder status: between-groups difference in estimated response rate at week 12. For CY-BOCS, NIMH-GOCS, and Clinical Global Impression Severity: between-groups difference in estimated mean score at week 12 divided by the pooled standard deviation of the outcome at week 12, otherwise known as Cohen *d*. A Cohen *d* score between 0.50 and 0.79 is considered a medium effect; Cohen *d* of 0.80 or higher is considered a large effect.[1] All effect size estimates are reported such that positive scores indicate that the first treatment group was superior to the comparison group in functioning.

Table 3. Adverse Events by Treatment Group

Adverse Event	Medication Management, No. of Patients			All Patients (N = 124)	*P* Value[a]
	Only (n = 42)	+Instruction in CBT (n = 40)	+CBT (n = 42)		
≥1	37	33	39	109	.36
≥1 that was drug related	20	14	21	55	.34
≥1 that led to study withdrawal	5	3	2	10	.48
Severe	1	1	0	2	.59

Abbreviation: CBT; cognitive behavior therapy.
[a] The reported *P* value was calculated with the use of Pearson χ^2 statistic.[1]

Post Hoc Analysis

Because medication management participants were more likely to prematurely terminate and receive additional treatment outside of their assigned treatment group, we conducted a post hoc analysis to investigate whether the conclusions of the main ITT findings would change if we accounted for individuals who received out-of-protocol treatment after premature termination. These analyses (eAppendix, available at http:www.jama.com) mirrored the ITT findings for all outcomes: the plus CBT was superior to the plus instructions in CBT and the medication management–only groups, with no difference between the plus instructions in CBT and the medication management–only groups.

Adverse Event Analyses

A summary of adverse event rates is reported in TABLE 3. No between-groups differences emerged on these variables. Two participants had serious adverse events during the study. One child in medication management made a suicide attempt during the trial, which led to a psychiatric hospitalization, premature termination, and changes to medication and therapy to better treat the child's comorbid depression. A child in the plus instructions in CBT reported suicidal thoughts during the last treatment visit due to teasing by classmates. Given the context in which these thoughts arose (eg, social difficulties at school), this seri-

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ous adverse event was determined to be unrelated to treatment.

COMMENT

Augmentation of maintenance SRI medication with CBT was efficacious, indicating that the combination of CBT and medication is superior to medication monotherapy whether delivered as acute treatment as in POTS I[7] or as augmentation. The magnitude of symptom reduction observed on the CY-BOCS was somewhat smaller than what was seen in the POTS I study of combined acute treatment; whether this reflects a sampling differences or a sequencing effect is unknown. Nevertheless, it is encouraging that CBT remained efficacious even in children and adolescents who had experienced partial response to medication treatment.

With respect to the potential utility of a brief form of CBT integrated into medication management, point estimates for medication management plus instructions in CBT showed improvement relative to medication management only, but there was insufficient evidence that these conditions differed on average on any of our primary or secondary outcome measures. Furthermore, although more patients in the medication management–only group dropped out or were prematurely terminated, secondary analyses suggested that the effect of medication management plus instructions in CBT remained small relative to medication management only. Reasons for the lack of a discernible effect may include lower intensity (brevity), less contact time with mental health clinician in plus instructions in CBT vs in the plus CBT, omission of key CBT components particularly in-session exposure exercises, inadequate treatment integrity, or some combination of these factors. The complex issue of treatment integrity will be examined in a comprehensive secondary article from our group; its absence herein represents a study limitation. Notably, although POTS II compared dual physician vs single-physician frameworks, the study provides no guidance about whether CBT for pediatric OCD should be provided by psychologists vs psychiatrists. Full CBT by a psychiatrist also providing medication management is a more than reasonable option for the family fortunate enough to find a CBT-trained child psychiatrist.

Sample heterogeneity with respect to treatment history and current medication resulted from an intentional design decision and reflected our primary interest in addressing the practical problem of partial response that affects many if not most pediatric patients with OCD treated in community settings. We believe that this sampling frame improves generalizability to such settings, although we acknowledge reduced experimental control over the potential effects of such variability. However, despite following recruitment strategies recommended by experts,[28] POTS II paralleled the broader OCD treatment literature in its failure to attract more than a few minority participants, which leaves unknown the applicability of our findings to these groups.

Findings from POTS I and II are consistent with a growing evidence base that supports the use of exposure plus response prevention as an initial or augmentative treatment for patients of all ages with OCD. Effectiveness studies conducted with samples across the age spectrum have indicated that good outcomes are not limited to highly selected randomized controlled trial samples[17] and can be achieved in community agencies by supervised therapists who are themselves not OCD experts.[32-34] Accordingly, these collective findings highlight the importance of disseminating CBT for pediatric OCD into community settings so that affected children have options beyond medication management alone. Furthermore, POTS II findings indicate that these dissemination efforts should focus on making the full CBT protocol more widely available in such settings rather than on attempting to create and disseminate truncated versions of this efficacious form of treatment. Toward these ends, research must focus on developing, evaluating, and comparing various models for disseminating CBT beyond the academic medical context.

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