

Randomized Trial of Behavior Therapy for Adults With Tourette Syndrome

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Context: Tics in Tourette syndrome begin in childhood, peak in early adolescence, and often decrease by early adulthood. However, some adult patients continue to have impairing tics. Medications for tics are often effective but can cause adverse effects. Behavior therapy may offer an alternative but has not been examined in a large-scale controlled trial in adults.

Objective: To test the efficacy of a comprehensive behavioral intervention for tics in adults with Tourette syndrome of at least moderate severity.

Design: A randomized controlled trial with posttreatment evaluations at 3 and 6 months for positive responders.

Setting: Three outpatient research clinics.

Patients: Patients (N=122; 78 males; age range, 16-69 years) with Tourette syndrome or chronic tic disorder were recruited between December 27, 2005, and May 21, 2009.

Interventions: Patients received 8 sessions of comprehensive behavioral intervention for tics or 8 sessions of supportive treatment for 10 weeks. Patients with a positive response were given 3 monthly booster sessions.

Main Outcome Measures: Total tic score on the Yale Global Tic Severity Scale and the Clinical Global Impression–Improvement scale rated by a clinician masked to treatment assignment.

Results: Behavior therapy was associated with a significantly greater mean (SD) decrease on the Yale Global Tic Severity Scale (24.0 [6.47] to 17.8 [7.32]) from baseline to end point compared with the control treatment (21.8 [6.59] to 19.3 [7.40]) ($P < .001$; effect size=0.57). Twenty-four of 63 patients (38.1%) were rated as much improved or very much improved on the Clinical Global Impression–Improvement scale compared with 4 of 63 (6.4%) in the control group ($P < .001$). Attrition was 13.9%, with no difference across groups. Patients receiving behavior therapy who were available for assessment at 6 months after treatment showed continued benefit.

Conclusion: Comprehensive behavior therapy is a safe and effective intervention for adults with Tourette syndrome.

Trial Registration: clinicaltrials.gov Identifier: NCT00231985

Arch Gen Psychiatry. 2012;69(8):795-803

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TOURETTE DISORDER, ALSO called Tourette syndrome (TS), is characterized by persistent motor and vocal tics.¹ The tics of TS are often rapid, jerky movements (eg, head jerks and facial movements) or vocalizations (eg, coughing and grunting) but may involve more complex movements and sounds (eg, skipping and repeating words).^{2,3} Tics begin in childhood, often peak in severity between the ages of 10 and 12 years, and decrease by early adulthood in many cases.^{2,4} Tourette syndrome affects an estimated 6 per 1000 school-age children.⁵ The prevalence of current TS is lower in adults, affecting an estimated 1 per 2000.⁶ Adults with TS report reduced quality of life,^{7,8} and those with coexisting attention-deficit/hyperactivity disorder (ADHD) are more

impaired than those with TS alone.⁹ Taken together, the persistence of tics in adults with TS reflects a chronic problem that is associated with disability.

The antipsychotic medications haloperidol and pimozide are approved for the treatment of tics in TS. However, many patients refuse or discontinue use of these drugs because of adverse effects (eg, dyskinesia, cognitive dulling, and sedation).¹⁰ The atypical antipsychotic risperidone is also effective in reducing tics.^{11,12} Although this medication is less likely to cause motor adverse effects compared with traditional antipsychotics, weight gain is an emerging concern for this and other medications in this class.¹⁰ Furthermore, pharmacotherapy rarely eliminates tics. Given the limitations of currently available medications, there is increasing interest in alternative and adjunctive treat-

ments to pharmacotherapy. The use of behavioral treatments for TS has been controversial.¹³ Expressed concerns include predictions of temporary improvements, tic rebound, tic symptom substitution, and unacceptable patient burden due to the effort required.^{14,15} Accumulating behavior therapy research based on habit reversal training challenges these concerns.¹⁶⁻²¹ The possibility that tics can be modified by behavioral intervention, however, does not contest the neurologic underpinnings of TS. Indeed, recent preclinical research^{22,23} indicates that learning plays an essential role in habitual motor behavior.

To date, the largest study²⁴ focused on tic reduction evaluated behavior therapy in 126 children with TS or chronic tic disorder (CTD). In this randomized trial, the comprehensive behavioral intervention for tics (CBIT) was superior to psychoeducation and supportive therapy (PST). The treatment was well tolerated, tic worsening was not observed, and treatment gains endured over time. The efficacy of behavioral interventions in adults has only been examined in small trials.²⁵ We conducted a multi-site study to evaluate the efficacy of CBIT compared with PST in adults with TS or CTD.

METHODS

STUDY DESIGN

This study was a 10-week randomized controlled trial comparing CBIT with PST. The primary outcome analysis evaluated the change in tic severity at week 10 (end of the acute treatment phase) assessed by an independent evaluator (a clinician masked to treatment assignment). Patients who showed a positive treatment response to either intervention received 3 monthly booster sessions and were invited to return for a follow-up assessment by the masked independent evaluator at 3 and 6 months after treatment to assess durability of treatment effects. Patients assigned to PST who did not show a positive response in the acute treatment phase were offered treatment with CBIT. By design, therefore, further comparison of randomized groups beyond week 10 was not possible.

The 3 recruitment sites for this study were Massachusetts General Hospital/Harvard Medical School, Yale University, and University of Texas Health Science Center at San Antonio. Training of independent evaluators, qualitative review of assessments, data management, and data analysis were provided by investigators at Yale University. Supervision of therapy was provided by investigators at Massachusetts General Hospital/Harvard Medical School, and quality of therapy was evaluated by investigators at the University of California at Los Angeles. The research was regularly reviewed by a data safety monitoring board and approved by the institutional review boards at each site. All adult participants and parents of minors provided consent; adolescents provided assent. The trial was registered at clinicaltrials.gov (NCT00231985).

STUDY PARTICIPANTS

Participants were recruited between December 27, 2005, and May 21, 2009, at 3 outpatient clinics located in major medical centers. In addition to direct enrollment from these clinics, recruitment strategies included flyers in public places, local clinician referrals, online postings, presentations at local patient meetings, and local newspaper and radio advertisements. The

Tourette Syndrome Association, a national consumer-based organization, also assisted with recruitment through direct mail and newsletter announcements.

To be eligible for the study, participants had to be at least 16 years old and meet diagnostic criteria for TS or CTD of moderate or greater severity based on a Clinical Global Impression–Severity score of 4 (moderate) or greater and a Yale Global Tic Severity Scale (YGTSS) total score greater than 14 (>10 for those with motor or vocal tics only).²⁶ Study participants had to be fluent in English and have an IQ greater than 80 on a standardized intelligence test. Patients with a history of schizophrenia or pervasive developmental disorder were excluded. The presence of a current or lifetime diagnosis of bipolar disorder, depression, anxiety disorder (including obsessive-compulsive disorder), or ADHD was acceptable for enrollment if the co-occurring disorder was stable and not in need of another treatment. Participants taking medication for tics had to be taking a stable dose for at least 6 weeks with no planned changes in medication type or dose for the duration of the study. For patients with a total tic score greater than 30 on the YGTSS, a cross-site panel reviewed the case to ensure that study participation was in their best interest. Patients with a current diagnosis of substance abuse or dependence were excluded. Finally, a history of 4 or more sessions of a similar behavioral treatment was exclusionary.

RANDOMIZATION

Eligible participants were randomized (using a computer algorithm) in a 1:1 ratio to CBIT or PST. The randomization was within site and stratified on the presence or absence of tic-suppressing medications. Patients and therapists were informed about the treatment assignment. Independent evaluators of treatment outcome were masked to treatment condition throughout all phases of the trial. Several methods were used to protect the treatment mask, including segregation of therapy and assessment records, separate therapist and independent evaluator teleconferences, and instruction to patients and family members to avoid discussing treatment assignment with the independent evaluators.

TREATMENTS

Both treatments consisted of 8 sessions for 10 weeks. The first 2 sessions were 90 minutes; subsequent sessions were 60 minutes. Sessions were held on a weekly basis, except for the last 2 sessions, which were spaced 2 weeks apart. Both interventions were designed as individual treatments; however, occasionally a spouse, significant other, or parent of a younger patient was included in the sessions. Patients who showed a positive response to either treatment at week 10 were invited to return for 3 monthly booster sessions and to participate in a follow-up assessment at 3 and 6 months after treatment.

Comprehensive behavioral intervention for tics²⁷ is an extension of habit reversal training. It includes an expanded set of strategies, such as psychoeducation about tic disorders, tic awareness training, competing response training, relaxation training, and functional analysis. Functional analysis identifies the events and situations that influence tic severity and develops strategies to manage these situations. Awareness training involves the detection of premonitory urges, which are sensations that precede the expression of the tic movement or vocalization.²⁸ Awareness training helps the patient intervene early, before engaging in the tic. Competing response training entails teaching the patient to engage in a behavior that is physically incompatible with the performance of the tic. For example, if a patient has the urge to engage in a shoulder tic, the

competing response might involve isometric tensing of arm muscles while pushing the elbow against the torso. Thus, the competing response encourages the patient to respond to the urge to tic in a new way. Over time, performance of the competing response breaks the cycle between the premonitory urge and the relief following the tic. The last 2 sessions focused on how to manage tic worsening or new tics.

Psychoeducation and supportive therapy provided disorder-specific information about the course, genetics, and underlying neurobiology of tic disorders and the rationale for current treatments. Participants were permitted to discuss tics and related issues, but therapists did not provide advice on strategies for tic management.

Therapists had a minimum of a master's degree in clinical psychology and were trained to reliability for both treatments, which were described in detailed treatment manuals. Therapists participated in weekly supervision via teleconference. On-site supervision was also available as needed. All treatment sessions were video-recorded, and 16% were randomly selected and independently rated for fidelity. The reviewer considered the prespecified central elements of the selected session for each treatment and then made a global rating (1-4 for poor, adequate, good, or excellent, respectively). The percentage of sessions rated good or better was 75.7% for CBIT and 87.7% for PST.

ASSESSMENT

Clinician-administered and self-report measures were completed before treatment to confirm eligibility and establish baseline symptom severity. The Structured Clinical Interview for DSM-IV²⁹ is a structured interview conducted by trained raters to assess a range of DSM-IV diagnoses. The Structured Clinical Interview for DSM-IV was augmented by the ADHD module from the Schedule for Affective Disorders and Schizophrenia for School-Age Children to assess current and past ADHD.³⁰ The primary outcome measures were the YGTSS²⁶ and Clinical Global Impression–Improvement (CGI-I) scale scores,³¹ which were repeated at week 5 and week 10 by an independent evaluator who was masked to treatment assignment.

The YGTSS is a clinician-rated scale used to assess tic severity and impairment due to tics.²⁶ Motor and vocal tics are rated separately from 0 to 5 on several dimensions (number, frequency, intensity, complexity, and interference). The scale yields a total score for motor tics (0-25), a total score for vocal tics (0-25), and a combined total tic score (0-50). The YGTSS impairment scale rates the overall burden associated with tics, and scores range from 0 to 50.

The CGI-I was used to measure overall treatment response. The scores range from 1 (very much improved) to 4 (no change) to 7 (very much worse). We defined positive response as a score of 1 or 2 (much improved or very much improved).

The Adult Tic Questionnaire (ATQ) is a self-report rating scale that is parallel in format and content to the Parent Tic Questionnaire.³² The ATQ asks individuals to report on the presence of 14 motor and 14 vocal tics during the past week. Tics that are present are then rated on a 0- to 3-point scale. The ATQ yields a motor tic score, a vocal tic score, and a total score. The internal consistency of the ATQ total score was favorable, with an α coefficient of .86 in this sample.

The masked independent evaluators who rated the YGTSS and the CGI scales had a master's degree or higher in a mental health care field. Before rating patients in the trial, the evaluators received training on the instruments and then demonstrated reliability on 3 video-recorded assessments. Ongoing supervision of raters was provided via biweekly cross-site teleconferences. All study interviews were recorded on video. An

18% sample of YGTSS interviews was randomly selected across baseline, week 5, and week 10 assessments for quality review using a 0- to 3-point scale on a 7-item scale, with higher scores reflecting better quality. An additional item rated overall quality on a 0- to 4-point scale. The mean (SD) score on the 7-item scale was 13.2 (2.96); the mean (SD) score on the overall quality item was 2.3 (0.90). These scores suggest good reliability, and there were no site differences.

ADVERSE EVENTS

The therapist inquired about adverse events at the start of each session. Therapists reviewed current health concerns, use of medication for any purpose, change in ongoing medication, and health care visits, including hospitalizations, for any reason. Patients could also offer spontaneous reports about any other problem. Endorsed concerns or medication changes prompted further discussion about the onset, severity, measures taken, and outcome of the adverse event. Adverse events were classified as mild, moderate, severe, or serious. Tic worsening was documented as an adverse event if the patient spontaneously reported an unexpected exacerbation. All documented adverse events were reviewed at the end of the study and classified into categories by type of concern by a clinician who was masked to treatment assignment.

STATISTICAL ANALYSIS

Baseline characteristics were compared between treatment groups with *t* tests for continuous variables and χ^2 tests for categorical variables. We proposed a minimally significant effect size of 0.55 to justify a sample size of 60 per group, presuming 10% attrition, a significance level of .05, and power of 80%. Efficacy analyses were conducted on all participants with at least 1 postrandomization visit in their assigned treatment condition. Outcome data are presented as least squares means from a mixed-model repeated-measures analysis, adjusted for site and baseline scores.^{33,34} This model assumes that missing data are missing at random and avoids the potential biases associated with analysis of completers only or using last observation carried forward.³⁵ The models included fixed effects for treatment (2 levels), time (5 and 10 weeks), site, time-by-treatment interaction, and a random effect for participant (using SAS PROC MIXED statistical software; SAS Institute, Inc). Sensitivity analyses, using the last observation carried forward, resulted in the same conclusions and are not presented. Using adjusted least squares mean values, we calculated effect sizes by subtracting the change on the YGTSS scores in PST from the change scores in CBIT divided by the SD for the entire study sample (N=122) at baseline. To examine whether the presence of tic medication at baseline or initial tic severity modified the effect of the treatment as measured on the YGTSS total tic score, we examined 2- and 3-way interactions of treatment with medication status and time, as well as the 2-way interaction of treatment with initial tic severity.

The proportion of patients with a positive response on the CGI-I scale was compared at week 10 using Fisher exact tests. Further exploratory analyses of the rate of positive response in subgroups defined by the presence of a tic medication and comparisons of adverse event rates were made using Fisher exact tests. Data regarding treatment durability were examined within each group using only those participants who showed a positive response at week 10 and returned for assessments at 3 and 6 months after treatment. All analyses were performed with SAS statistical software, version 9.2 (SAS Institute, Inc), at the 2-sided .05 level of significance. No adjustment was made for multiple comparisons for testing secondary outcomes.

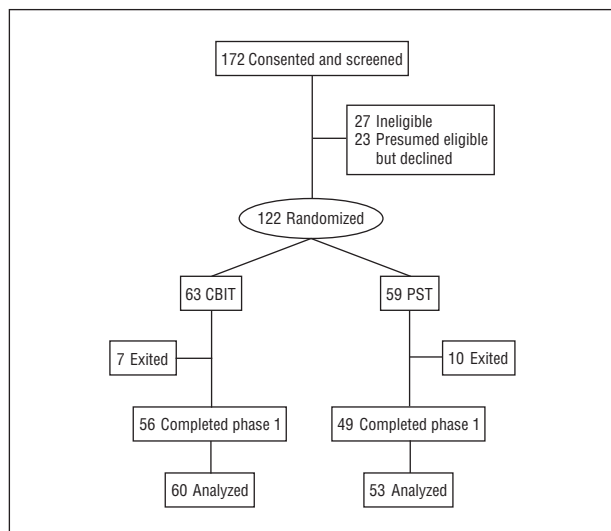


Figure. Flow of patients through the study. CBIT indicates comprehensive behavioral intervention for tics; PST, psychoeducation and supportive therapy.

RESULTS

BASELINE CHARACTERISTICS

One hundred seventy-two patients were screened and 122 randomly assigned to CBIT ($n=63$) or PST ($n=59$) (**Figure**). Six patients exceeded the threshold score of 30 on the YGTSS total tic score; 3 were enrolled and 3 were excluded after review by the cross-site panel. Attrition was not significantly different between treatments, with 11.1% (7 of 63) for the behavioral intervention group and 17.0% (10 of 59) for the control treatment.

Enrollment across the 3 sites was similar. Patients ranged in age from 16 to 69 years (mean [SD], 31.6 [13.7] years); 78 (63.9%) were male, 98 (80.3%) were white, and 103 (84.4%) met criteria for TS. Overall, 31 patients (25.4%) entered the trial taking a stable tic medication (17 patients [27.0%] in the CBIT group and 14 patients [23.7%] in the PST group). No significant between-group differences were found in baseline demographic or clinical characteristics, including tic medication status³⁶ (**Table 1**).

Patients in the CBIT group attended 87.9% of scheduled sessions compared with 86.7% in the control group. During the 10-week trial, 1 participant in the PST group reported a change in tic medication; no patients in the CBIT group reported a change in a tic medication.

OUTCOMES

After 10 weeks of treatment, CBIT was superior to control treatment in reducing the YGTSS total tic score ($P < .001$, effect size=0.57), with a 25.8% decrease from baseline to week 10 compared with a 11.5% decrease for the control treatment (**Table 2**). Neither the presence of tic-suppressing medication at baseline nor initial tic severity moderated treatment outcome as measured by the YGTSS total tic score. The effect size for the YGTSS motor tic score was 0.63 ($P = .002$) and 0.35 on the YGTSS vocal tic score

Table 1. Baseline Demographic and Clinical Characteristics by Treatment Group^a

Characteristic	CBIT (n = 63)	PST (n = 59)
Age, mean (SD), y	31.6 (13.5)	31.5 (14.1)
Mean WTAR IQ, mean (SD)	108.6 (11.5)	107.9 (14.8)
Male sex	38 (60.3)	40 (67.8)
Occupation ^b		
Student	20 (31.7)	20 (34.0)
Unemployed	6 (9.5)	3 (5.1)
Laborer, homemaker, clerical	8 (12.7)	10 (17.0)
Craftsman, technical	7 (11.1)	8 (13.6)
Professional	21 (33.3)	17 (28.8)
Missing	1 (1.6)	1 (1.7)
Educational level		
Partial high school	13 (20.6)	14 (23.7)
High school	6 (9.5)	6 (10.2)
Technical school or some college	13 (20.6)	15 (25.4)
College graduate	25 (39.7)	14 (23.7)
Graduate or professional school	6 (9.5)	10 (16.9)
Race/ethnicity		
White, non-Hispanic	48 (76.2)	50 (84.7)
White, Hispanic	11 (17.5)	6 (10.2)
Black	0	1 (1.7)
Asian/Pacific Islander	4 (6.3)	1 (1.7)
Other	0	1 (1.7)
Marital status		
Never married	42 (66.7)	34 (57.6)
Married	15 (23.8)	21 (35.6)
Other	6 (9.5)	4 (6.8)
Living arrangement		
Lives alone	13 (20.6)	5 (8.5)
Lives with partner	20 (31.7)	24 (40.7)
Lives with parents	19 (30.2)	22 (37.3)
Other	11 (17.5)	8 (13.6)
Tic disorder		
Tourette disorder	55 (87.3)	48 (81.4)
Chronic motor tic	7 (11.1)	11 (18.6)
Chronic vocal tic	1 (1.6)	0
Attention-deficit/hyperactivity disorder ^c	17 (27.0)	17 (28.8)
Obsessive-compulsive disorder	13 (23.6)	9 (15.3)
Major depressive episode	10 (15.9)	14 (23.7)
Generalized anxiety	6 (9.5)	5 (8.5)
Social phobia	1 (1.6)	3 (5.1)
Panic disorder	1 (1.6)	2 (3.4)
Substance use disorder	4 (6.3)	5 (8.5)
Bipolar disorder	0	3 (5.1)
Other diagnoses ^d	16 (25.4)	20 (33.9)
Medication status ^e		
No medication	46 (73.0)	45 (76.3)
Antipsychotic	5 (7.9)	6 (10.2)
α -Agonist	6 (9.5)	4 (6.8)
Anticonvulsant	0	2 (3.4)
Benzodiazepine	2 (3.2)	0
Antipsychotic and α -agonist	2 (3.2)	0
Antipsychotic and anticonvulsant	1 (1.6)	1 (1.7)
Antipsychotic and benzodiazepine	0	1 (1.7)
Other	1 (1.6)	0

Abbreviations: CBIT, comprehensive behavioral intervention for tics; PST, psychoeducation and supportive therapy; WTAR, Wechsler Test of Adult Reading.³⁶

^aData are presented as number (percentage) of patients unless otherwise indicated.

^bNo significant between-group differences were found for any of the listed variables.

^cSome patients had more than 1 coexisting diagnosis.

^dOther diagnoses include dysthymia, specific phobia, eating disorders (eg, anorexia, bulimia, and binge eating), trichotillomania, posttraumatic stress disorder, and somatization.

^eAntipsychotics included haloperidol, pimozide, risperidone, aripiprazole, and fluphenazine; α -agonist included guanfacine and clonidine; anticonvulsants included valproate sodium and topiramate; and benzodiazepines included clonazepam.

Table 2. Baseline and Week 10 Scores on Key Outcome Measures^a

Yale Global Tic Severity Scale	Mean (SD)		Mean Group Difference for Week 10 (95% CI) ^b	P Value	Effect Size (Corrected for PST)
	CBIT (n = 63)	PST (n = 59)			
Total tic score					
Baseline	24.0 (6.5)	21.8 (6.6)	...		
Week 5	21.5 (6.6)	20.2 (6.5)	0.5 (-0.9 to 1.9)		
Week 10	17.8 (7.3)	19.3 (7.4)	3.3 (1.4 to 5.2)	<.001	0.6
Within-group effect size	1.0	0.4	...		
Total motor					
Baseline	15.4 (3.4)	14.9 (3.0)	...		
Week 5	14.1 (3.1)	13.9 (3.3)	0.1 (-0.8 to 1.0)		
Week 10	11.7 (3.5)	13.2 (4.1)	1.8 (0.7 to 2.8)	.002	0.6
Within-group effect size	1.2	0.5	...		
Total vocal					
Baseline	8.6 (4.9)	6.8 (5.3)	...		
Week 5	7.5 (4.9)	6.4 (5.1)	0.2 (-0.8 to 1.3)		
Week 10	6.1 (5.2)	6.2 (5.3)	1.4 (0.1 to 2.6)	.03	0.4
Within-group effect size	0.5	0.1	...		
Impairment					
Baseline	23.8 (6.2)	24.5 (7.4)	...		
Week 5	18.9 (8.8)	20.9 (9.8)	1.6 (-1.6 to 4.7)		
Week 10	14.7 (9.7)	18.8 (10.9)	3.9 (0.5 to 7.2)	.03	0.5
Within-group effect size	1.4	0.8	...		
ATQ total score					
Baseline	41.2 (24.7)	36.6 (23.3)	...		
Week 5	32.3 (22.2)	34.2 (23.0)	5.1 (0.1 to 10.1)		
Week 10	26.2 (20.6)	30.0 (22.0)	7.5 (1.9 to 13.0)	.001	0.4
Within-group effect size	0.6	0.3	...		

Abbreviations: ATQ, Adult Tic Questionnaire; CBIT, comprehensive behavior therapy for tics; PST, psychoeducation and supportive therapy.

^aData are presented as least square means (SDs) for baseline, week 5, and week 10. Group differences at week 10 with P values and effect sizes are also presented. Effect sizes corrected for PST were estimated by subtracting the 10-week baseline-adjusted least squares mean changes in the control group from the mean change in the CBIT group and dividing by the SD for the entire study sample (N = 122) at baseline. Within-group effect sizes were calculated by subtracting the 10-week baseline-adjusted least squares mean changes in each group and dividing the SD as previously mentioned.

^bDifferences in means were adjusted for site and baseline outcomes.

(P = .03). The behavioral intervention also demonstrated superiority to the control treatment on the YGTSS impairment scale (Table 2), with a 38.2% decrease from baseline to week 10 compared with a 23.3% decrease for the control treatment (P = .03, effect size = 0.50).

The rate of positive treatment response as evidenced by a masked evaluator's rating of much improved or very much improved on the CGI-I scale was significantly higher for CBIT (24 of 63 [38.1%]) vs PST (4 of 59 [6.8%]) (P < .001, Fisher exact test; number needed to treat = 5). For participants taking stable tic medication (at least 6 weeks before randomization and no planned changes during the trial), 4 of 17 (23.5%) in the CBIT group showed a positive response compared with 1 of 14 (7.1%) in the PST group (P = .34, Fisher exact test; number needed to treat = 6). For participants not taking a tic medication, the rate of positive response was 43.5% (20 of 46) for the CBIT group compared with 6.7% (3 of 45) for the PST group (P < .001, Fisher exact test; number needed to treat = 3). Within the CBIT group, the rate of positive response in patients not taking a tic medication compared with those taking tic medication was clearly larger but not statistically significant (P = .24, Fisher exact test).

On the self-rated ATQ, CBIT was associated with a 40% improvement on the total score compared with 12.2% in the PST group (P = .001; effect size = 0.35) (Table 2).

ADVERSE EVENTS

Two hundred twenty-four adverse events were reported during the 10-week trial. Of these, 71 (31.7%) were rated mild, 134 (59.8%) moderate, and 19 (8.5%) severe. **Table 3** presents the adverse events by group that occurred more often than 5%. In addition, there were 3 serious adverse events (elbow fracture requiring surgery in the PST group, hospitalization for chest pain in the CBIT group, and exacerbation of diverticulitis requiring hospitalization also in the CBIT group). These unexpected adverse events are unlikely to be related to either study intervention. Greater-than-usual tic worsening was reported by 4 patients (6.3%) in the CBIT group and by 4 (6.8%) in the control group (Table 3).

TREATMENT DURABILITY

Patients showing a positive response to either treatment in the short-term treatment phase were reevaluated at 3 and 6 months after treatment. Of the 24 patients showing a positive response to CBIT in the 10-week trial, 15 (62.5%) returned for follow-up at 3 and 6 months after treatment. Two of 4 patients (50.0%) showing a positive response to PST returned for follow-up assessments. At 6 months, 12 of the 15 available patients (80.0%) in the CBIT group showed continued benefit, and 1 of 4

Table 3. Adverse Events During the 10-Week Randomized Trial Occurring More Often Than 5%

Adverse Event ^a	Adverse Events, No.		P Value ^b
	CBIT (n = 63)	PST (n = 59)	
Muscle or joint pain	18	21	.44
Headache	11	16	.28
Rhinitis	10	7	.61
Anxiety or depression	10	17	.13
Sleep problems	9	3	.13
Upper gastrointestinal problem	7	4	.53
Irritability	0	6	.01
Upper respiratory tract infection	6	8	.58
Dermatological problems	6	5	.99
Allergy	6	7	.77
Sore throat	5	4	.99
Tic worsening	4	4	.99

^aDefined as mild (new event that did not interfere with activities of daily living), moderate (new event that posed some interference or required intervention to prevent interference), or severe (new event that posed interference and required intervention).

^bFisher exact test.

(25.0%) of those in the control group showed continued benefit (**Table 4**). These results suggest that the benefits of behavior therapy are stable over time.

COMMENT

Compared with PST, CBIT was associated with a significant reduction in tics and tic-related impairment. These results validate smaller studies in adults.^{20,21} The rate of positive response in this study (38.1%) was lower than the 52.5% observed in a previous trial of CBIT in children.²⁴ Noting that many children with TS show a decrease in tics by early adulthood,⁴ adults with enduring tics may have a more chronic form of the disorder. This more chronic condition may require more intensive treatment than the 8 sessions offered in this trial.

The absolute decrease in the total tic score of the YGTSS in the CBIT group was lower than the decrease observed in some placebo-controlled medication trials in TS^{12,37-39} on this same outcome measure. Compared with the mean 25.8% decrease in the current study, these trials reported improvements ranging from 32.3% to 53.6% (with decreases in placebo ranging from 6.9% to 17.3%). Several other medication trials, with sample sizes ranging from 10 to 61, showed smaller percentage decreases on the YGTSS and were not superior to placebo.⁴⁰ The somewhat smaller decrease in the current study compared with other positive placebo-controlled trials was not unexpected. First, with few exceptions, these drug trials enrolled pediatric patients. Indeed, a previous CBIT trial in children showed a 30.8% decrease in the YGTSS score.²⁴ Second, unlike the current trial, most placebo-controlled drug trials enrolled medication-free patients. Although the presence of tic medication at baseline did not moderate treatment in the current trial, the estimated number needed to treat was higher for those taking tic medication compared with those not taking tic medication. Noting that there was no difference in base-

Table 4. Patients Showing Continued Positive Response on the CGI-I Scale at 3 and 6 Months After Treatment

Follow-up Period	Positive Response at Follow-up, No. (%)	
	Available Patients ^a	All Possible Patients Showing a Positive Response
CBIT		
3 Months	13/15 (86.7)	13/24 (54.2)
6 Months	12/15 (80.0)	12/24 (50.0)
Control treatment		
3 Months	1/2 (50.0)	1/4 (25.0)
6 Months	1/2 (50.0)	1/4 (25.0)

Abbreviations: CBIT, comprehensive behavior therapy for tics; CGI-I, Clinical Global Impression-Improvement.

^aThe proportion of patients showing continued positive response over available participants and all short-term treatment responders. Status of patients lost to follow-up is unknown, and these individuals are not counted as positive responders.

line tic severity by tic medication status, tic severity at baseline does not appear to explain the somewhat more favorable response for patients not taking a tic medication. Assuming that tic medication attenuated baseline tic severity, it is difficult to disentangle medication status from tic severity. Thus, conclusions about tic severity and treatment outcome from this study are limited. Future exploratory analyses of our current data may clarify which patients are most likely to show a positive or negative response to CBIT. A future trial could enroll medication-free patients across a range of tic severity to evaluate the effect of baseline tic severity on CBIT treatment outcome.

The rate of attrition (13.9%) was not different across treatment groups (CBIT and PST). Compared with several recent placebo-controlled medication trials of similar duration, this rate of attrition was higher than one trial¹² but lower than others.^{39,41} In addition, patients attended nearly 90% of scheduled sessions. Therapist fidelity, which was rigorously monitored with independent rating of randomly selected sessions, was commendable, with more than 80% of reviewed sessions rated good or better. Taken together, these findings indicate that CBIT can be reliably delivered by therapists, and it is acceptable to patients with TS. Moreover, these findings are not consistent with the claim that CBIT requires extraordinary effort from patients.⁴² Given the multisite design, our results also suggest that CBIT is an exportable treatment. The obvious next step is wider dissemination of CBIT.²⁷ The Tourette Syndrome Association is actively engaged in this effort (<http://www.tsa-usa.org>).

Participants and therapists were not masked, suggesting the possibility of bias in favor of CBIT. However, we chose PST because it is similar to what experienced therapists provide to patients with TS in the community. The low rate of attrition and the high rate of session attendance further suggest that PST was acceptable and meaningful to patients.

Adverse events, including tic worsening, were monitored throughout the trial. Four patients in each treatment group reported tic worsening during the 10-week trial. Thus, CBIT instructions to increase awareness of

tics and premonitory urges and to engage in a voluntary competing response were not associated with tic worsening. This observation, as well as a similar observation in a previous CBIT trial in children, refutes the concern that increased attention to tics will cause an increase in tics.^{14,43} Although a wide range of other adverse events were reported during the trial, no differences were found between CBIT and PST. Collectively, these results indicate that CBIT was well tolerated and, with regard to adverse events, no different from supportive therapy, a commonly offered adjunctive treatment in TS.⁴⁴

Medication has been the mainstay for treating tics for more than 40 years.¹⁰ Although the pathophysiology of tics is not completely understood, it appears to involve subtle dysregulation of the motor system.^{23,45,46} Our results suggest that CBIT is a viable alternative to other TS treatments. Given the limited medication options and the adverse effects associated with antipsychotic medications and the risks of more extreme treatments, such as deep brain stimulation for the treatment of tics,^{13,47} additional treatment options with favorable adverse effect profiles are warranted. Future research focused on the mechanism of CBIT may uncover the role of learning in reducing the involuntary movements and vocalizations of TS.

Submitted for Publication: June 15, 2011; final revision received September 20, 2011; accepted October 1, 2011.

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Financial Disclosure: Drs Wilhelm, Peterson, Piacentini, Woods, Deckersbach, Chang, Walkup, and Scahill report receiving royalties from Oxford University Press for a treatment manual on tic disorders. Drs Wilhelm, Peterson, Piacentini, Woods, Chang, Sukhodolsky, Walkup, and Scahill report receiving honoraria for continuing education presentations from the Tourette Syndrome Association. Drs Piacentini, Woods, and Walkup receive royalties from Guilford Press for a book on Tourette disorder. Dr Wilhelm reports receiving support in the form of free medication and matching placebo from Forest Laboratories for clinical trials funded by the National Institutes of Health and receiving book royalties from Guilford Publications, New Harbinger Publications, and Oxford University Press and speaking honoraria from PRIMEDIA Healthcare, a publicly traded company working as a logistics collaborator for the Massachusetts General Hospital Psychiatry Academy (the education programs conducted by the Massachusetts General Hospital Psychiatry Academy were supported through independent medical education grants from pharmaceutical companies cosupporting the overall program, along with participant tuition). Dr Piacentini reports receiving royalties from Oxford University Press for treatment manuals on child obsessive-compulsive disorder and American Psychological Association Books for other books on child mental health, speaking honoraria from Janssen-Cilag, and support in the form of free medication and matching placebo from Pfizer for clinical trials funded

by the National Institute of Mental Health. Dr Woods reports receiving book royalties from New Harbinger and Springer Publications. Dr Scahill has received royalties from Oxford University Press and American Psychiatric Press; has served as a consultant for Boehringer-Ingelheim, Biomarin, Hoffman NeuroSearch, and Pfizer; and has had research support from Shire Pharmaceutical and Seaside Therapeutics. He also reports receiving support in the form of free medication and matching placebo from Shire Pharmaceuticals for a clinical trial funded by the National Institute of Mental Health. Dr Deckersbach reports receiving consulting fees from the Constella Group for serving as a reviewer for the Department of Defense's Congressionally Directed Medical Research Program. He also reports receiving honoraria, consulting fees, and/or royalties from Medacorp, Massachusetts General Hospital Psychiatry Academy, BrainCells Inc, Systems Research and Applications Corp, Boston University, the Catalan Agency for Health Technology Assessment and Research, and the National Association of Social Workers–Massachusetts. He reports participating in research funded by Janssen, Forest Research Institute, Shire Development Inc, Medtronic, Cyberonics, and Northstar. Dr Walkup reports receiving consulting fees from Eli Lilly and JAZZ Pharmaceuticals and lecture fees from CMP Media, Medical Education Reviews, McMahon Group, DiMedix, and the Tourette Disorder Association. He reports receiving free drug and matching placebo from Pfizer and Lilly and free drugs from Abbott for National Institute of Mental Health–funded clinical trials. He reports receiving fees for consultation with defense counsel and submission of written reports in litigation involving GlaxoSmithKline.

Funding/Support: This work was supported by grants 5R01MH069877 (Dr Wilhelm), R01MH069874 (Dr Scahill), and R01MH069875 (Dr Petersen) from the National Institute of Mental Health with subcontracts to Drs Piacentini and Woods. Dr Walkup consulted on this grant. Drs Scahill and Dziura receive support from the Yale University Clinical and Translational Sciences Award grant UL1 RR024139 from the National Center for Research Resources, National Institutes of Health. This study was also supported by Tourette Syndrome Association funding to Dr Scahill.

Role of the Sponsor: The funding organization had no role in the design or conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Previous Presentation: Some results described in this article were presented at the Annual Meeting of the Association for Behavioral and Cognitive Therapies; November 20, 2009; New York, New York.

Additional Information: The following individuals participated and were compensated for participation in this study: site principal investigators: Sabine Wilhelm, PhD (Massachusetts General Hospital/Harvard Medical School), Lawrence Scahill, MSN, PhD (Yale Child Study Center and School of Nursing), and Alan L. Peterson, PhD (University of Texas Health Science Center at San Antonio); study coinvestigators: Thilo Deckersbach, PhD (Massachusetts General Hospital/Harvard Medical School)

and Denis Sukhodolsky, PhD (Yale Child Study Center) (K Award K01 MH079130); consultant: John T. Walkup, MD (Johns Hopkins Medical Institutions); study coordinators/research assistants: Diane Findley, PhD (supervising coordinator), and Joseph McGuire, BA, Allison Gavaletz, BA (Yale Child Study Center), Dieu-My Phan, MSW, LCSW, Katherine Crowe, BA, Shana Franklin, BA, and Theresa Rowley, BA (Massachusetts General Hospital); Christin Pasker, MS, and Robert Villarreal, MS (University of Texas Health Science Center); therapists: Meredith Charney, PhD, Luana Marques, PhD, Hannah Reese, PhD, Jedidiah Siev, PhD, Ulrike Buhlmann, PhD, and Kiara Timpano, PhD (Massachusetts General Hospital), Denis Sukhodolsky, PhD (Yale Child Study Center), and Trisha Benson, MA, Stephanie Bezner, PhD, Lisa Cavanagh, PsyD, Meredith Draper, PhD, Orion Mosko, PhD, Jeslina Raj, PsyD, Geetanjali Sharma, MS, and Ashley Williams, PhD (University of Texas Health Science Center); independent evaluators: Antoinette Brundige, MS (University of Texas Health Science Center), Anne Chosak, PhD (Massachusetts General Hospital), and Maryellen Pachler, MSN, and Lawrence Scahill, MSN, PhD (Yale University); data center: Lawrence Scahill, MSN, PhD, James Dziura, PhD, Lily Katsovich, MS, MBA, Joseph McGuire, BA, Cynthia Brandt, MD, and Stephanie Argraves, MS (Yale University); recruitment/meeting support: Judit Ungar, MSW, Sue Levi-Pearl, MA, Heather Cowley, PhD, and Julie Noulas (Tourette Syndrome Association); and editorial support: Julie R. Collins, BS (University of Texas Health Science Center).

Additional Contributions: We thank the National Institute of Mental Health for supporting this study and the patients who participated. We also thank Gerald Golden, MD, and Kevin Black, MD, for their service on the Data and Safety Monitoring Board. The Data Safety Monitoring Board members received an honorarium for their consultation.

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