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Randomized Trial of Behavior Therapy for Adults with Tourette's Disorder

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Abstract

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Context—Tics in Tourette syndrome begin in childhood, peak in early adolescence, and often decline 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.

Subjects—Subjects (N = 122; 78 males, age 16 to 69 years) with Tourette syndrome or chronic tic disorder.

Interventions—Eight sessions of Comprehensive Behavioral Intervention for Tics or 8 sessions of supportive treatment delivered over 10 weeks. Subjects showing a positive response were given 3 monthly booster sessions.

Main Outcome Measures—Total Tic score of the Yale Global Tic Severity Scale and the Improvement scale of the Clinical Global Impression rated by a clinician blind to treatment assignment.

Results—Behavior therapy was associated with a significantly greater decrease on the Yale Global Tic Severity Scale (24.0 ± 6.47 to 17.8 ± 7.32) from baseline to endpoint compared to the control treatment (21.8 ± 6.59 to 19.3 ± 7.40) ($P < .001$; effect size = 0.57). Twenty-four of 63 subjects (38.1%) in CBIT were rated as *Much Improved* or *Very Much Improved* on the Clinical Global Impression-Improvement scale compared to 6.8% (4 of 63) in the control group ($P < .0001$). Attrition was 13.9% with no difference across groups. Subjects in behavior therapy available for assessment at 6 months posttreatment showed continued benefit.

Conclusions—Comprehensive behavior therapy is a safe and effective intervention for adults with Tourette syndrome.

INTRODUCTION

Tourette's disorder, also called Tourette syndrome (TS), is characterized by persistent motor and vocal tics.[1] The tics of TS are often rapid, jerky movements (e.g., head jerks, facial movements) or vocalizations (e.g., coughing, grunting), but may involve more complex movements and sounds (e.g., skipping, repeating words).[2,3] Tics begin in childhood, often peak in severity between ages 10 and 12, and decline by early adulthood in many cases.[2,4] TS 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 decline or discontinue use of these drugs due to adverse effects (e.g., dyskinesia, cognitive dulling, sedation).[10] The atypical antipsychotic risperidone is also effective in reducing tics.[11,12] Although this medication is less likely to cause motor side effects compared to 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 treatments 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 neurological underpinnings of TS. Indeed, recent preclinical research indicates that learning plays an essential role in habitual motor behavior.[22,23]

To date, the largest study focused on tic reduction evaluated behavior therapy in 126 children with TS or chronic tic disorder.[24] In this randomized trial, the comprehensive behavioral intervention for tics was superior to supportive psychotherapy. 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 multisite study to evaluate the efficacy of a comprehensive behavioral intervention for tics compared to supportive psychotherapy in adults with TS or chronic tic disorder.

METHODS

Design

This was a 10-week randomized controlled trial comparing comprehensive behavior therapy for tics (CBIT) with psychoeducation and supportive therapy (PST). The primary outcome analysis evaluated the change in tic severity at Week 10 (end of acute treatment phase) assessed by an independent evaluator (a clinician blinded to treatment assignment). Subjects 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 blinded independent evaluator at 3 and 6 months posttreatment to assess durability of treatment effects. Subjects assigned to PST who did not show a positive response in the acute 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 The 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 on clinicaltrials.gov (NCT00231985).

Participants

Participants were recruited between December 2005 and May 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, as well as 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 chronic tic disorder (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 subjects with motor or vocal tics only).[26] Subjects had to be fluent in English and have an intelligence quotient greater than 80 on a standardized intelligence test. Subjects 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 attention deficit hyperactivity disorder was acceptable for enrollment if the co-occurring disorder was stable and not in need of another treatment. Participants on a medication for tics had to be on a stable dose for at least 6 weeks with no planned changes in medication type or dose for the duration of the study. For subjects 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. Subjects 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. Subjects and therapists were informed about the treatment assignment. Independent evaluators of treatment outcome were blinded to treatment condition throughout all phases of the trial. Several methods were used to protect the treatment blind, including segregation of therapy and assessment records, separate therapist and independent evaluator teleconferences, and instruction to subjects and family members to avoid discussing treatment assignment with the independent evaluators.

Treatments

Both treatments consisted of 8 sessions over 10 weeks. The first 2 sessions were 90 minutes long; subsequent sessions were 60 minutes long. 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 a parent of a younger patient was included in sessions. Subjects 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 posttreatment.

CBIT[27] 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, prior to 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 subject 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.

PST provided disorder-specific information about the course, genetics and underlying neurobiology of tic disorders, as well as 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 on 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 to 4 for poor, adequate, good or excellent). 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 pretreatment to confirm eligibility and establish baseline symptom severity. The Structured Clinical Interview for DSM-IV (SCID)[29] is a structured interview conducted by trained raters to assess a range of DSM-IV diagnoses. The SCID 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 Yale Global Tic Severity Scales (YGTSS),[26] and Clinical Global Impression-Improvement (CGI-I) scale,[31] which were repeated at Week 5 and Week 10 by an independent evaluator who was blind 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 to 25), a total score for vocal tics (0 to 25); and a combined Total Tic score (0 to 50). The YGTSS Impairment scale rates the overall burden associated with tics and score range from 0-50.

The Clinical Global Impression scale for Improvement (CGI-I) was used to measure overall treatment response. The scores range from 1 (very much improved) through 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 subjects to report on the presence of 14 motor and 14 vocal tics over the past week. Tics that are present are then rated on a 0 to 3 scale. The ATQ yields a motor tic score, vocal tic score, and a total score. The internal consistency of the ATQ total score was favorable with an alpha coefficient 0.86 in this sample.

The blinded independent evaluators who rated the YGTSS and the CGI scales had a master's degree or higher in a mental health field. Prior to rating subjects in the trial, these clinicians 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 scale on a 7-item scale with higher scores reflecting better quality. An additional item rated overall quality on a 0 to 4 scale. The mean score on the 7-item scale was 13.2 ± 2.96; the mean 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 complaints, use of medication for any purpose, change in ongoing medication, and health care visits including hospitalizations for any reason. Subjects could also offer spontaneous reports about any other problem. Endorsed complaints 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 subject spontaneously reported an unexpected exacerbation. All documented adverse events were reviewed at the end of the study and classified into categories by type of complaint, blind to treatment assignment.

Statistical Analysis

Baseline characteristics were compared between treatment groups with *t*-tests for continuous variables and chi-square 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, significance level of 5% 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). 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 standard deviation 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 subjects with a positive response on the CGI-I scale was compared at Week 10 using Fisher's 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's 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 posttreamtent. All analyses were performed with SAS Version 9.2 (Cary, NC) at the 2-sided 0.05 level of significance. There was no adjustment for multiple comparisons for testing secondary outcomes.

RESULTS

Baseline Characteristics

One hundred seventy-two subjects were screened and 122 randomly assigned to CBIT (n = 63) or PST (n = 59) (see Figure 1). A total of 6 subjects exceeded the threshold score of 30 on the YGTSS Total Tic score; 3 were enrolled and 3 were excluded following review by the cross-site panel. Attrition was not significantly different between treatments with 11% (7 of 63) for the behavioral intervention group and 17% (10 of 59) for the control treatment.

Enrollment across the 3 sites was similar. Subjects ranged in age from 16 to 69 years (mean = 31.6 ± 13.7 years); 78 (64%) were male, 98 (80%) were Caucasian, and 103 (84%) met criteria for TS. Overall, 26% of subjects entered the trial on a stable tic medication (25% in CBIT; 27% in PST). There were no significant between-group differences in baseline demographic or clinical characteristics, including tic medication status (Table 1).

Subjects in the behavior therapy intervention attended 87.9% of scheduled sessions compared to 86.7% for the control condition. During the 10-week trial, 1 participant in PST reported a change in tic medication; no subjects in CBIT reported change in a tic medication.

Outcomes

After 10 weeks of treatment, CBIT was superior to control treatment in reducing YGTSS Total Tic score (P <.001, effect size = 0.57), with a 26% decline from baseline to Week 10 compared to a 12% decline for the control treatment (see Figure 2 and 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 (P = .03). The behavioral intervention also demonstrated superiority to the control treatment on the YGTSS Impairment scale (see Table 2) with a 36% decline from baseline to Week 10 compared to a 22% decline for the control treatment (P = .03, effect size = 0.50).

The rate of positive treatment response as evidenced by a blinded evaluator's rating of *much improved* or *very much improved* on the CGI-Improvement scale was significantly higher for CBIT (38.1%; 24 of 63) versus PST (6.8%; 4 of 59) (Fisher Exact P < .0001; number-needed-to-treat = 5). For participants on stable tic medication (at least 6 weeks prior to randomization and no planned changes during the trial), 23.5% (4 of 17) in the CBIT group showed a positive response compared to 7.1% (1 of 14) in the PST group (Fisher Exact P = .34; number-needed-to-treat = 6). For participants not on a tic medication, the rate of positive response was 43.5% (20 of 46) for CBIT compared to 6.7% (3 of 45) in PST (Fisher Exact P < .0001; number-needed-to-treat = 3). Within the CBIT group, the rate of positive response in subjects not on a tic medication compared to those on tic medication was clearly larger, but not statistically significant (Fisher Exact P = .24).

On the self-rated Adult Tic Questionnaire, CBIT was associated with a 40% improvement on the total score compared to 12.2% in the PST group (P = .001; effect size = 0.35) (see 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 (see Table 3). There were 3 serious adverse events (elbow fracture requiring surgery in PST, hospitalization for chest pain in CBIT, exacerbation of diverticulitis requiring hospitalization also in CBIT). These unexpected adverse events are unlikely to be related to either study intervention. Greater-than-usual tic worsening was reported by 4 (6.3%) subjects in the behavioral intervention group and by 4 (6.8%) in the control treatment (see Table 3).

Treatment Durability

Subjects showing a positive response to either treatment in the acute phase were re-evaluated at 3 and 6 months posttreatment. Of the 24 subjects showing a positive response to CBIT in the 10-week trial, 15 (63%) returned for follow up at 3 and 6 months posttreatment. Two of 4 (50%) subjects showing a positive response to PST returned for follow-up

assessments. At 6 months, 12 of the 15 (80%) available subjects in the CBIT group showed continued benefit and 1 of 4 (25%) of those in the control group showed continued benefit. These results suggest that the benefits of behavior therapy are stable over time.

DISCUSSION

CBIT was associated with a significant reduction in tics and tic-related impairment compared to PST. These results validate smaller studies in adults.[20,21] The rate of positive response in this study (38%) was lower than the 52% observed in our previous trial of CBIT in children.[24] Noting that many children with TS show a decline in tics by early adulthood,[4] adults with enduring tics may represent 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 on the Total Tic score of the Yale Global Tic Severity Scale (YGTSS) in the CBIT group was lower than the decrease observed in some placebo-controlled medication trials in TS[12,36-38] on this same outcome measure. Compared to the mean 26% decrease in the current study, these trials reported improvements ranging from 30% to 50% (with declines in placebo ranging from 7% to 20%). Several other medication trials, with sample sizes ranging from 10 to 61, showed smaller percent decreases on the YGTSS and were not superior to placebo.[39] The somewhat smaller decrease in the current study compared to other positive placebo-controlled trials was not unexpected. First, with few exceptions, these drug trials enrolled pediatric subjects. Indeed, our previous CBIT trial in children showed a 31% decline in the YGTSS.[24] Second, unlike the current trial, most placebo-controlled drug trials enrolled medication-free subjects. 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 on tic medication compared to those not on tic medication. Noting that there was no difference in baseline tic severity by tic medication status, tic severity at baseline does not appear to explain the somewhat more favorable response for subjects not on 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 subjects are most likely to show a positive or negative response to CBIT. A future trial could enroll medication-free subjects across a range of tic severity to evaluate the impact of baseline tic severity on CBIT treatment outcome.

The rate of attrition (13.9%) was not different across treatment groups (CBIT and PST). Compared to several recent placebo-controlled medication trials of similar duration, this rate of attrition was higher than one trial,[12] but lower than others.[38,40] In addition, subjects attended nearly 90% of scheduled sessions. Therapist fidelity, which was rigorously monitored with independent rating of randomly selected sessions, was commendable with over 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.[41] Given the multi-site 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 blinded 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 subjects 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 our previous CBIT trial in children, refutes the concern that increased attention to tics will cause an increase in tics.[14,42] Although a wide range of other adverse events were reported during the trial, there were no differences 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.[43]

Medication has been the mainstay for treating tics for over 40 years.[10] Although the pathophysiology of tics is not completely understood, it appears to involve subtle dysregulation of the motor system.[23,44,45] 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,[13,46] 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.

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REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed.. American Psychiatric Association; Washington, DC: 2000. text rev. (DSMIV-TR)
2. Leckman, JF.; Bloch, MH.; King, RA.; Scahill, L. Phenomenology of tics and natural history of tic disorders. In: Walkup, JT.; Mink, JW.; Hollenbeck, PJ., editors. Advances in Neurology: Tourette Disorder. Vol. 99. Lippincott Williams & Wilkins; Philadelphia, PA: 2006. p. 1-16.
3. Woods, DW.; Piacentini, JC.; Walkup, JT., editors. Treating Tourette Syndrome and Tic Disorders. Guilford Press; New York, NY: 2007.
4. Bloch MH, Leckman JF. Clinical course of Tourette syndrome. J Psychosom Res. 2009; 67(6):497–501. [PubMed: 19913654]
5. Khalifa N, von Knorring A. Prevalence of tic disorders and Tourette Disorder in a Swedish school population. Dev Med Child Neurol. 2003; 45(5):315–319. [PubMed: 12729145]
6. Apter A, Pauls DL, Bleich A, Zohar AH, Kron S, Ratzoni G, Dycian A, Kotler M, Weizman A, Gadot N, Cohen DJ. An epidemiologic study of Gilles de la Tourette's syndrome in Israel. Arch Gen Psychiatry. 1993; 50(9):734–738. [PubMed: 8357298]
7. Eddy CM, Cavanna AE, Gulisano M, Agodi A, Barchitta M, Calì P, Robertson MM, Rizzo R. Clinical correlates of quality of life in Tourette syndrome. Mov Disord. 2011; 26(4):735–738. [PubMed: 21506153]
8. Elstner K, Selai CE, Trimble MR, Robertson MM. Quality of Life (QOL) of patients with Gilles dela Tourette's syndrome. Acta Psychiatrica Scandinavica. 2001; 103(1):52–59. [PubMed: 11202129]
9. Haddad AD, Umoh G, Bhatia V, Robertson MM. Adults with Tourette's syndrome with and without attention deficit hyperactivity disorder. Acta Psychiatrica Scandinavica. 2009; 120(4):299–307. [PubMed: 19486328]
10. Scahill L, Erenberg G, Berlin CM Jr, Budman C, Coffey BJ, Jankovic J, Kiessling L, King RA, Kurlan R, Lang A, Mink J, Murphy T, Zinner S, Walkup J. Tourette Syndrome Association Medical Advisory Board: Practice Committee. Contemporary assessment and pharmacotherapy of Tourette syndrome. NeuroRx. 2006; 3(2):192–206. [PubMed: 16554257]

11. Dion Y, Annable L, Sandor P, Chouinard G. Risperidone in the treatment of Tourette syndrome: a double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2002; 22(1):31–39. [PubMed: 11799340]
12. Scahill L, Leckman J, Schultz R, Katsovich L, Peterson B. A placebo-controlled trial of risperidone in Tourette syndrome. Neurology. 2003; 60(7):1130–1135. [PubMed: 12682319]
13. Kurlan R. Clinical practice. Tourette's syndrome. N Engl J Med. 2010; 363(24):2332–2338. [PubMed: 21142535]
14. Burd L, Kerbeshian J. Treatment-generated problems associated with behavior modification in Tourette disorder. Dev Med Child Neurol. 1987; 29(6):831–833. [PubMed: 3480256]
15. Franklin SA, Walther MR, Woods DW. Behavioral interventions for tic disorders. Psychiatr Clin North Am. 2010; 33(3):641–655. [PubMed: 20599138]
16. Himle MB, Woods DW. An experimental evaluation of tic suppression and the tic rebound effect. Behav Res Ther. 2005; 43(11):1443–1451. [PubMed: 16159587]
17. Himle MB, Woods DW, Conelea CA, Bauer CC, Rice KA. Investigating the effects of tic suppression on premonitory urge ratings in children and adolescents with Tourette's syndrome. Behav Res Ther. 2007; 45(12):2964–2967. [PubMed: 17854764]
18. Azrin NH, Peterson AL. Habit reversal for the treatment of Tourette Syndrome. Behav Res Ther. 1988; 26(4):347–351. [PubMed: 3214400]
19. Azrin NH, Peterson AL. Treatment of Tourette Syndrome by habit reversal: a waiting-list control group comparison. Behav Ther. 1990; 21(3):305–318.
20. Deckersbach T, Rauch S, Buhlmann U, Wilhelm S. Habit reversal versus supportive psychotherapy in Tourette's disorder: a randomized controlled trial and predictors of treatment response. Behav Res Ther. 2006; 44(8):1079–1090. [PubMed: 16259942]
21. Wilhelm S, Deckersbach T, Coffey BJ, Bohne A, Peterson AL, Baer L. Habit reversal versus supportive psychotherapy for Tourette's disorder: a randomized controlled trial. Am J Psychiat. 2003; 160(6):1175–1177. [PubMed: 12777279]
22. Graybiel, A.; Canales, J. The neurobiology of repetitive behaviors: clues to the neurobiology of Tourette Disorder. In: Cohen, DJ.; Jankovic, J.; Goetz, C., editors. Advances in Neurology: Tourette Disorder. Vol. 99. Lippincott Williams & Wilkins; Philadelphia, PA: 2001. p. 123-132.
23. Taylor JL, Rajbhandari AK, Berridge KC, Aldridge JW. Dopamine receptor modulation of repetitive grooming actions in the rat: potential relevance for Tourette syndrome. Brain Res. 2010; 1322:92–101. [PubMed: 20114036]
24. Piacentini J, Woods DW, Scahill L, Wilhelm S, Peterson AL, Chang S, Ginsburg GS, Deckersbach T, Dziura J, Levi-Pearl S, Walkup JT. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA. 2010; 303(19):1929–1937. [PubMed: 20483969]
25. Peterson, AL. Psychosocial management of tics and intentional repetitive behaviors associated with Tourette Disorder. In: Woods, DW.; Piacentini, JC.; Walkup, JT., editors. Treating Tourette Disorder and Tic Disorders: A Guide for Practitioners. Guilford Press; New York, NY: 2007. p. 154-184.
26. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, Cohen DJ. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adol Psychiat. 1989; 28(4):566–573.
27. Woods, DW.; Piacentini, JC.; Chang, SW.; Deckersbach, T.; Ginsburg, GS.; Peterson, AL.; Scahill, LD.; Walkup, JT.; Wilhelm, S. Managing Tourette's Syndrome: A Behavioral Intervention for Children and Adults (Therapist Guide). Oxford University Press; New York, NY: 2008.
28. Leckman JF, Walker DE, Cohen DJ. Premonitory urges in Tourette's syndrome. Am J Psychiatry. 1993; 150(1):98–102. [PubMed: 8417589]
29. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P, Version 2.0). Biometrics Research Dept, New York State Psychiatric Institute; New York, NY: 1995.
30. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version

(K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997; 36(7):980–988. [PubMed: 9204677]

31. Guy, W.; Bonato, R., editors. CGI: Clinical Global Impressions. National Institute of Mental Health; Chevy Chase, MD: 1970.
32. Chang S, Himle M, Woods D, Tucker B, Piacentini J. Initial psychometric properties of a brief parent-report instrument for assessing tic severity in children with chronic tic disorders. Child Fam Beh Ther. 2009; 31(3):181–191.
33. Brown, H.; Prescott, R. Applied Mixed Models in Medicine. John Wiley & Sons; Chichester, England: 1999.
34. Carpenter, JR.; Kenward, MG. Missing Data in Randomised Controlled Trials: A Practical Guide. National Institute for Health Research; Birmingham, England: 2007. Available at http://www.pcpoh.bham.ac.uk/publichealth/methodology/projects/RM03_JH17_MK.shtml [Accessed May 17, 2011]
35. Allison, PD. Missing Data: University Papers Series on Quantitative Applications in the Social Sciences. Sage; Thousand Oaks, CA: 2001.
36. Sallee FR, Kurlan R, Goetz CG, Singer H, Scahill L, Law G, Dittman VM, Chappell PB. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. J AmAcad Child Adolesc Psychiatry. 2000; 39(3):292–299.
37. Gilbert DL, Dure L, Sethuraman G, Raab D, Lane J, Sallee FR. Tic reduction with pergolide in a randomized controlled trial in children. Neurology. 2003; 60(4):606–611. [PubMed: 12601100]
38. Jankovic J, Jimenez-Shahed J, Brown LW. A randomised, double-blind, placebo-controlled study of topiramate in the treatment of Tourette syndrome. J Neurol Neurosurg Psychiatry. 2010; 81(1): 70–73. [PubMed: 19726418]
39. Scahill, L.; King, RA.; Lombroso, PJ.; Sukhodolsky, DG.; Leckman, JF. Assessment and treatment of Tourette syndrome and other tic disorders. In: Martin, A.; Scahill, L.; Kratochvil, CJ., editors. Pediatric Psychopharmacology Principles and Practice. 2nd ed.. Oxford University Press; New York, NY: 2011. p. 516-530.
40. De Jonge JL, Cath DC, van Balkom AJ. Quetiapine in patients with Tourette's disorder: an open-label, flexible-dose study. J Clin Psychiatry. 2007; 68(7):1148–1150. [PubMed: 17685760]
41. Jeffrey, S.; Nghiem, HT. Medscape CME Clinical Briefs. Children with Tourette's syndrome and chronic tic disorders respond to behavioral therapy. http://www.medscape.org/viewarticle/722270?src=cmenews. Released May 24, 2010 [Accessed December 26, 2010]
42. Shimberg, EF. Living with Tourette Syndrome. Simon & Schuster; New York, NY: 1995.
43. Goetz, C.; Horn, S. The treatment of tics. In: Kurlan, R., editor. Handbook of Tourette's Syndrome and Related Tic and Behavioral Disorders. 2nd ed.. Marcel Dekker; New York, NY: 2005. p. 411-426.
44. Marsh R, Maia TV, Peterson BS. Functional disturbances within frontostriatal circuits across multiple childhood psychopathologies. Am J Psychiatry. 2009; 166(6):664–674. [PubMed: 19448188]
45. Mink, JW. Neurobiology of basal ganglia and Tourette syndrome: Basal ganglia circuits and thalamocortical outputs. In: Walkup, JT.; Mink, JW.; Hollenbeck, PJ., editors. Advances in Neurology: Tourette syndrome. Vol. 99. Lippincott Williams & Wilkins; Philadelphia, PA: 2006. p. 89-98.
46. Swain JE, Scahill L, Lombroso PJ, King RA, Leckman JF. Tourette syndrome and tic disorders: a decade of progress. J Am Acad Child Adolesc Psychiatry. 2007; 46(8):947–968. [PubMed: 17667475]

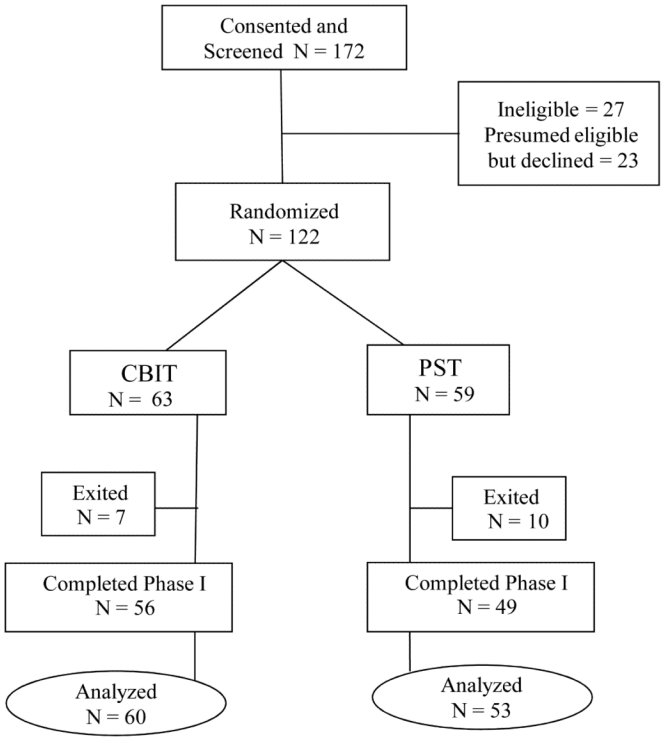

Figure 1. Subject Flow

Table 1
Baseline Demographic and Clinical Characteristics by Treatment Group*

Variable	CBIT (N = 63)		PST (N = 59)	
Age (M, SD)	31.6	(13.5)	31.5	(14.1)
Mean WTAR IQ (M, SD)	108.6	(11.5)	107.9	(14.8)
Male Gender (N, %)	38	(60.3)	40	(67.8)
Occupation (N, %) *				
Laborer/Homemaker/Clerical	2	(3.2)	3	(5.1)
Craftsperson/Artist/Technician	2	(3.2)	3	(5.1)
Self-Employed	4	(6.3)	0	(0)
Professional	15	(23.8)	15	(25.4)
Education (N, %)				
Partial High School	13	(20.6)	14	(23.7)
High School	6	(9.5)	6	(10.2)
Technical School/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 (N, %)				
White (Non-Hispanic)	48	(76.2)	50	(84.7)
White (Hispanic)	11	(17.5)	6	(10.2)
Black	--	--	1	(1.7)
Asian/Pacific Islander	4	(6.3)	1	(1.7)
Other	--	--	1	(1.7)
Marital Status (N, %)				
Never Married	42	(66.7)	34	(57.6)
Married	15	(23.8)	21	(35.6)
Other	6	(9.5)	4	(6.8)
Living Arrangement (N, %)				
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 (N, %)				
Tourette Disorder	55	(87.3)	48	(81.4)
Chronic Motor Tic	7	(11.1)	11	(18.6)
Chronic Vocal Tic	1	(1.6)	0.0	(0.0)
Attention Deficit Hyperactivity Disorder †	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)

Variable	CBIT (N = 63)		PST (N = 59)	
Substance Use Disorder	4	(6.3)	5	(8.5)
Bipolar Disorder	0		3	(5.1)
Other Diagnoses ≠	16	(25.4)	20	(33.9)
Medication Status (N, %)≠				
No Medication	46	(73.0)	45	(76.3)
Antipsychotic	5	(7.9)	6	(10.2)
Alpha Agonist	6	(9.5)	4	(6.8)
Anticonvulsant	0	0	2	(3.4)
Benzodiazepine	2	(3.2)	0	0
Antipsychotic + Alpha Agonist	2	(3.2)	0	0
Antipsychotic + Anticonvulsant	1	(1.6)	1	(1.7)
Antipsychotic + Benzodiazepine	0	0	1	(1.7)
Other	1	(1.6)	0	0

*There were no significant between-group differences for any of the listed variables.

†Lifetime diagnoses, some subjects had more than one coexisting diagnosis.

≠Other diagnoses include Dysthymia, Specific Phobia, Eating Disorders (Anorexia, Bulimia, Binge eating), Trichotillomania, PTSD and Somatization.

≠Antipsychotics: haloperidol, pimozide, risperidone, aripiprazole, fluphenazine; Alpha Agonist: guanfacine, clonidine; Anticonvulsants: valproate, topiramate; Benzodiazepines: clonazepam.

Table 2

Baseline and Week 10 Scores on Key Outcome Measures *

	CBIT (N = 63)		PST (N = 59)		Group Difference Wk10 Mean (95% CI)**	*P* value	Effect Size (Corrected for PST)
	Mean	**(SD)**	**Mean**	**(SD)**			
Yale Global Tic Severity Scale							
Total Tic Score							
Baseline	24.0	(6.47)	21.8	(6.59)			
Week 5	21.5	(6.56)	20.2	(6.52)	0.5(−0.9−1.9)		
Week 10	17.8	(7.32)	19.3	(7.40)	3.3(1.4-5.2)	<0.001	0.57
Within Group Effect Size	0.96		0.39				
Total Motor							
Baseline	15.4	(3.45)	14.9	(3.01)			
Week 5	14.1	(3.09)	13.9	(3.34)	0.1 (−0.8−1.0)		
Week 10	11.7	(3.50)	13.2	(4.09)	1.8(0.7-2.8)	0.002	0.63
Within Group Effect Size	1.15		0.53				
Total Vocal							
Baseline	8.6	(4.91)	6.8	(5.34)			
Week 5	7.5	(4.87)	6.4	(5.11)	0.2(−0.8,1.3)		
Week 10	6.1	(5.15)	6.2	(5.29)	1.4(0.1-2.6)	0.03	0.35
Within Group Effect Size	0.49		0.12				
Impairment							
Baseline	23.8	(6.21)	24.5	(7.41)			
Week 5	18.9	(8.80)	20.9	(9.75)	1.6(−1.6−4.7)		
Week 10	14.7	(9.72)	18.8	(10.90)	3.9(0.5-7.2)	0.03	0.50
Within Group Effect Size	1.35		0.84				
ATQ Total Score							
Baseline	41.2	(24.71)	36.6	(23.28)			
Week 5	32.3	(22.23)	34.2	(22.98)	5.1(0.1-10.1)		
Week 10	26.2	(20.65)	30.0	(22.04)	7.5(1.9-13.0)	0.001	0.35
Within Group Effect Size	0.63		0.28				

ATQ = Adult Tic Questionnaire

*Data are presented as least square mean values and standard deviations 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 standard deviation 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 standard deviation as above.

** Differences in means were adjusted for site and baseline outcomes.

Table 3
Count of Adverse Events During the 10-Week Randomized Trial

Adverse Event*	CBIT (N = 63) n (%)	PST (N = 59) n (%)	*P* value
Muscle or joint pain	18	21	0.44
Headache	11	16	0.28
Rhinitis	10	7	0.61
Anxiety/depression	10	17	0.13
Sleep problems	9	3	0.13
Upper gastrointestinal problem	7	4	0.53
Irritability	0	6	0.01
Upper respiratory Infection	6	8	0.58
Dermatological problems	6	5	0.99
Allergy	6	7	0.77
Sore throat	5	4	0.99
Tic worsening	4	4	0.99

*Defined 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)

†Fisher's Exact test.

Table 4

Subjects Showing Continued Positive Response on the CGI-I at 3 Months and 6 Months Posttreatment

	Positive Response at Follow-up			
	Available Subjects		All Possible Subjects Showing a Positive Response	
Follow-up Period	N † (%)	(%)	N	(%)
CBIT				
Three Months	13/15	86.7%	13/24	54.2%
Six Months	12/15	80%	12/24	50%
Control Treatment				
Three Months	1/2	50%	1/4	25%
Six Months	1/2	50%	1/4	25%

† The proportion of subjects showing continued positive response over available participants and all acute-phase responders. Status of subjects lost to follow-up is unknown and not counted as positive responders.