A Placebo-Controlled Trial of Cognitive-Behavioral Therapy and Clomipramine in Trichotillomania

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Background: The major treatments reported to be effective in the treatment of trichotillomania are cognitive-behavioral therapy (CBT) with habit reversal and serotonin-norepinephrine reuptake inhibitors such as clomipramine. However, the 2 treatments have not been previously compared with each other. This study examines the efficacy of CBT and clomipramine compared with placebo in the treatment of trichotillomania.

Method: Twenty-three patients with trichotillomania as determined by the Structured Clinical Interview for DSM-III-R entered and 16 completed a 9-week, placebo-controlled, randomized, parallel-treatment study of CBT and clomipramine. Efficacy was evaluated by the Trichotillomania Severity Scale, the Trichotillomania Impairment Scale, and the Clinical Global Impressions-Improvement scale, which were conducted by an independent assessor blinded to the treatment condition.

Results: CBT had a dramatic effect in reducing symptoms of trichotillomania and was significantly more effective than clomipramine ($p = .016$) or placebo ($p = .026$). Clomipramine resulted in symptom reduction greater than that with placebo, but the difference fell short of statistical significance. Placebo response was minimal.

***Conclusion*:** Clinicians should be aware of the potential treatments available for trichotillomania. A larger and more definitive study comparing CBT and a serotonin-norepinephrine reuptake inhibitor is indicated.

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Trichotillomania is characterized by a recurrent failure to resist impulses to pull out one's hair, resulting in noticeable hair loss.[1] It affects mostly females, with a prepubertal age at onset in the majority of individuals. Trichotillomania is estimated to be highly prevalent in the population, and it can cause significant distress and social impairment.[2] Trichotillomania is classified as an impulse-control disorder, although it is also considered as part of a spectrum of obsessive-compulsive disorders.[3,4]

Cognitive-behavioral therapy (CBT) with habit reversal[5] and serotonin-norepinephrine reuptake inhibitors like clomipramine[6] are the only treatments reported to be effective in controlled studies for trichotillomania, but they have not been previously compared with one another in a controlled investigation. This study sought to compare CBT with clomipramine in a randomized, placebo-controlled trial.

METHOD

All patients provided informed consent after an explanation of the study procedures and possible effects. Patients were evaluated clinically for eligibility. The Structured Clinical Interview for DSM-III-R (SCID-R)[7] was administered by a clinician; baseline evaluation was performed by an independent assessor. Patients were randomly assigned to 1 of 3 conditions: CBT, clomipramine, or placebo. Clomipramine and placebo were prescribed in a double-blind manner. Treatment consisted of 9 weekly sessions during which patients randomly assigned to clomipramine and placebo saw a psychiatrist and patients randomly assigned to CBT saw a behavioral psychologist. All patients were charged a fee for each visit, based on capacity to pay, with medication being provided free. Patients randomly assigned to placebo received an active treatment of their choice, free of charge, for an equivalent period after the study. Pretreatment and posttreatment assessments were conducted by an independent assessor blinded to the treatment condition. The independent assessor functioned off-site to maintain the treatment blind and hence was unavailable for unscheduled visits, including early terminations.

Patients

Of the 23 patients entered, 7 patients (30%) failed to complete the study and did not have blinded ratings at study termination. Four (40%) of 10 patients receiving clomipramine, 2 (29%) of 7 receiving CBT, and 1 (17%) of 6 receiving placebo were noncompleters (Fisher exact test for association between completers and noncompleters, p = .846). Of the 4 noncompleters receiving clomipramine, 1 lost her job precipitously and moved 3 weeks prior to completion and was lost to subsequent care (her last Clinical Global Impressions-Improvement [CGI-I][8] assessment was rated as 2, much improved, by her treating clinician), and the other 3 discontinued because of significant side effects. Of the CBT noncompleters, 1 failed to keep her first appointment, and the other dropped out after 8 sessions (she was rated as 3, minimally improved, on the CGI-I by her clinician). One patient receiving placebo was lost to follow-up early in her treatment. Patients who failed to complete the study did not differ from the completers in comorbid Axis I diagnoses, severity of depression, state anxiety, or severity of and impairment from trichotillomania symptoms. Noncompleters were replaced to maintain balanced cells among completers.

The final sample of 16 patients comprised 13 women (81.3%). Fourteen (87.5%) were white, and 2 (12.5%) were African American. The mean ± SD age was 33.38 ± 9.09 years (range, 22–53 years) with a mean ± SD duration of hair pulling of 20.62 ± 9.12 years (range, 10–40 years). The mean ± SD pretreatment Beck Depression Inventory (BDI)[9] score was 8.13 ± 8.33 and State-Trait Anxiety Inventory (STAI)[10] state score was 41.29 ± 10.10. The sites of pulled hair were scalp (75%), eyelashes (44%), eyebrows (25%), pubic (25%), and other (19%).

Medication

Weekly sessions with the psychiatrist (P.T.N.) lasted approximately 20 minutes. Each patient received clomipramine, 50 mg, or placebo pills. Patients started receiving one 50-mg pill or placebo at bedtime, and the dosage was increased as tolerated until clinical benefit, up to a maximum of 250 mg. Patients were offered general encouragement and support along with monitoring of clinical status and medication effects. No specific cognitive or behavioral therapy was provided.

The mean daily dose of clomipramine achieved in patients receiving clomipramine was 116.7 mg. Three patients experienced no side effects. Prominent side effects (moderate or severe intensity) were tremor (N = 3 patients), sedation (N = 2), dry mouth (N = 2), constipation (N = 2), memory difficulty (N = 1), and nausea (N = 1). One patient receiving placebo had a moderate increase in appetite. Three of the 10 patients randomly assigned to clomipramine failed to achieve the desired minimum dose of 100 mg/day owing to side effects. The mean daily dose of placebo achieved was the equivalent of 250 mg.

Cognitive-Behavioral Therapy

CBT included the complete habit reversal package tested by Azrin et al.,[5] stimulus control, and a stress management component developed by Veronen and Kilpatrick[11] and tested for posttraumatic stress disorder by Foa et al.[12] Session 1 focused on information gathering, including response description, response detection (awareness training), identifying response precursors (early warning), identifying habit-prone situations, and self-monitoring. Session 2 began habit reversal training, which included the rationale for treatment, habit inconvenience review, competing response practice, prevention training, and symbolic rehearsal. Stimulus control was also begun at this time either to decrease opportunities to pull hair or to interfere with or prevent pulling. Self-monitoring continued throughout treatment, and the therapist continued information gathering for a general assessment. Sessions 3 through 9 included training in stress management skills, including deep muscle relaxation, differential relaxation plus breathing retraining, thought-stopping, Beck/Ellis cognitive restructuring, guided self-dialogue (e.g., preparing for a stressor), covert modeling and role play, and relapse prevention. CBT was delivered by a clinical psychologist (B.O.R.) in 9 weekly 45-minute sessions. The treatment provided has been published as a treatment manual.[13]

Measures

Assessments included the Trichotillomania Severity Scale (TSS) and the Trichotillomania Impairment Scale (TIS),[6] the CGI-I, the BDI, and the STAI.

The National Institute of Mental Health (NIMH) Trichotillomania Severity and Impairment Scales were developed by Swedo et al.[6] These instruments yield a severity score (TSS) and an impairment score (TIS). The severity score comprises 5 questions assessing aspects of trichotillomania, including frequency, resistance, intensity, distress, and interference, each rated on a scale of 0 to 5. The TSS is the sum of scores on these questions, ranging from 0 to 25. The impairment scale ranges from 0 to 10 and is based on the resulting damage from hair pulling, time spent in pulling or concealing damage, and ability to control pulling. On both scales, higher scores indicate more severity. The scores are based primarily on self-report with clinical corroboration based on the degree of hair loss. Detailed psychometrics for the TSS are not available. However, it was derived from the Yale-Brown Obsessive Compulsive Scale, a 10-item scale that rates severity of obsession and compulsion in obsessive-compulsive disorder (OCD).[6] The measures have been sensitive to change in symptoms with treatment.[14]

Statistics

Efficacy of treatment was tested using the TSS, TIS, and CGI-I as outcome measures. Efficacy on the TSS and

Table 1. Means (95% confidence intervals [CI]), Repeated-Measures ANOVA Statistics, and Post Hoc (Scheffé) Comparisons of TSS and TIS Scores for Completers[a]

	CBT (N = 5)		Clomipramine (N = 6)		Placebo (N = 5)		Statistics		
Measure	Pre	Post	Pre	Post	Pre	Post	F (df = 2,13)	p Value	Contrasts[b]
TSS									
Mean	15.6	1.6	15.2	9.3	13.7	12.3	11.0	.002	CBT > placebo,
95% CI	8.1 to 23.1	–2.6 to 5.8	8.3 to 22.0	5.5 to 13.2	6.2 to 21.2	8.1 to 16.5			CBT > clomipramine
TIS									
Mean	6.8	1.6	8.0	5.8	5.6	4.2	7.6	.006	CBT > placebo,
95% CI	4.0 to 9.6	–1.3 to 4.5	5.4 to 10.6	3.2 to 8.5	2.8 to 8.4	1.3 to 7.1			CBT > clomipramine

[a]Abbreviations: ANOVA = analysis of variance, CBT = cognitive-behavioral therapy, TIS = Trichotillomania Impairment Scale, TSS = Trichotillomania Severity Scale.
[b]Significant post hoc contrasts of improvement in scores ($p < .05$).

TIS was assessed using repeated-measures analysis of variance (ANOVA) statistics and post hoc (Scheffé) comparison of the different treatments. For the CGI-I, responders (defined a priori as those scoring < 2 on the CGI-I, i.e., very much improved or much improved) to the different treatments were examined using the Fisher exact test. All statistical tests were 2-tailed.

RESULTS

Pretreatment and posttreatment means, 95% confidence intervals, and statistical results are presented in Table 1. Severity (as measured by the TSS) and impairment (as measured by the TIS) were significantly reduced from pretreatment to posttreatment ($p = .002$ and $p = .006$, respectively). Post hoc analysis indicated that CBT produced significantly more change ($p < .05$) than placebo and clomipramine on both severity and impairment.

On the CGI-I (Table 2), the percentage of responders to CBT (100% of completers, 71% of intent-to-treat subjects) was significantly higher than for placebo (0% responders) and clomipramine (67% of completers, 40% of intent-to-treat subjects). Clomipramine produced more responders than did placebo, approaching conventional levels of significance ($p = .061$).

Table 2. Distribution of Clinical Global Impressions-Improvement (CGI-I) Scores and Tests of Treatment Differences for Completers[a]

	CGI-I Score[b]							Fisher Exact Test, p Value	
Treatment	1	2	3	4	5	6	7	vs Clomipramine	vs CBT
CBT, N	4	1	0	0	0	0	0	.026	n/a
Clomipramine, N	0	4	2	0	0	0	0	n/a	.026
Placebo, N	0	0	4	0	1	0	0	.061	.016

[a]Fisher exact test for the complete table: $p = .0009$. Abbreviation: n/a = not applicable.
[b]CGI-I scores: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

DISCUSSION

This is an exploratory study of acute treatments for trichotillomania. Given the number of patients, any significant findings would suggest a large effect size. Both active treatments were effective in reducing severity of hair pulling, while placebo did not have any significant benefits. CBT had a dramatic effect and achieved statistical significance versus the other 2 treatments. Four of the 5 CBT completers were essentially free of symptoms by posttreatment, and the fifth patient had sufficient reduction in symptoms to meet the a priori categorical definition of response.

Although clomipramine was effective in reducing symptoms of trichotillomania, given the low power, it failed to achieve conventional levels of significance. Of the 6 clomipramine-treated patients who completed the trial, 4 were categorized as responders. Preliminary data from another cohort suggest that clomipramine response can be predicted by baseline cerebrospinal fluid 5-HIAA levels, potentially explaining clomipramine response heterogeneity.[15] Unlike the CBT responders, none of the responders to clomipramine were symptom-free. The average dose of clomipramine achieved was relatively low due to side effects that also resulted in a high dropout rate. Trichotillomania patients seemed to exhibit a greater sensitivity to the side effects of clomipramine than OCD patients, who comprised fewer noncompleters in a controlled study than did trichotillomania patients in this one.[16] Higher doses in this study could potentially have resulted in greater benefits, and the inability to use higher doses in this study supports the need for trials with other serotonin-norepinephrine reuptake inhibitors with a more advantageous side effect profile.[17] The pharmacologic management of trichotillomania remains a challenge because of the lack of consistent clinical response to a variety of agents in both clinical practice and clinical trials.[18]

Placebo did not produce any significant clinical change (mean CGI-I score rated between 3, minimally improved, and 4, no change). The lack of placebo response indicates that the active treatments accounted for the change noted rather than contact with a therapist, at-

tention paid to hair pulling, paying for treatment, or any external/historical factors.

The strengths of the study include random assignment of patients, blind independent assessment of symptoms, comparison of the 2 state-of-the-art treatments conducted by experts in the field, placebo control, and adequate treatment length. Some of the limitations of this study include the small sample size, which limits the generalizability of the findings, and measurement of symptoms. The assessment of trichotillomania symptoms is problematic.[19] Subjective report and observation of alopecia provide the basis of current assessment. Although the independent assessor was blinded to the treatments provided, patients receiving CBT were not, and they could have biased the judgment of the independent assessor to a different degree from patients in the double-blind condition. However, the similarity of the current findings with those in the literature lends support to the validity of these results.

The acute response to CBT and a serotonin-norepinephrine reuptake inhibitor needs to be explored further in a controlled design with a larger sample. Continuation and maintenance treatments remain to be systematically explored.

Drug name: clomipramine (Anafranil and others).

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