A Randomized, Double-Blind, Placebo-Controlled Trial of Olanzapine in the Treatment of Trichotillomania

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Background: Trichotillomania has been considered as part of the obsessive-compulsive disorder spectrum; however, trichotillomania treatment with obsessive-compulsive disorder medications has largely been unsuccessful.

Objective: To determine whether a dopaminergic treatment as used in tics and Tourette's syndrome would be effective in trichotillomania.

Method: Twenty-five participants with *DSM-IV* trichotillomania participated in a 12-week, randomized, double-blind, placebo-controlled trial of flexible-dose olanzapine for trichotillomania. Recruitment occurred between August 2001 and December 2005, and follow-up was completed in February 2006. The primary outcome measure was the Clinical Global Impressions-Improvement (CGI-I) scale, and secondary measures of efficacy included the Yale-Brown Obsessive Compulsive Scale for Trichotillomania (TTM-YBOCS) and the Clinical Global Impressions-Severity of Illness (CGI-S) scale.

Results: Eleven of 13 participants (85%) in the olanzapine group and 2 of 12 (17%) in the placebo group were considered responders according to the CGI-I ($P = .001$). There was a significant change from baseline to end point in the TTM-YBOCS ($P < .01$) and the CGI-S ($P < .001$). The mean ± SD dose of olanzapine at end point was 10.8 ± 5.7 mg/d. Twenty-one of 25 patients (84%) reported at least 1 adverse event, but no adverse events resulted in early withdrawal from the study.

Conclusion: Olanzapine seems to be a safe and effective treatment for primary *DSM-IV* trichotillomania.

Trial Registration: clinicaltrials.gov Identifier: NCT00182507

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Trichotillomania is classified as an impulse control disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*).[1] Reported lifetime prevalence rates range from 0.6% to 3.4%.[2] Trichotillomania affects women more than men (3:1).[3] The mean age at onset has been estimated at approximately 13 years in studies of adult populations.[4]

There is some controversy as to the most appropriate conceptualization of trichotillomania. It has been suggested that trichotillomania may lie on an obsessive-compulsive spectrum of disorders, which share similar phenomenology and neurobiologic underpinnings.[5–8] The obsessive-compulsive spectrum disorders are characterized as being similar to obsessive-compulsive disorder (OCD) on the basis of features such as age at onset, clinical course and comorbidity, presumed etiology, familial transmission, and response to certain pharmacologic treatments (eg, selective serotonin reuptake inhibitors [SSRIs]).[9,10]

There appears to be a high lifetime prevalence of trichotillomania among OCD patients.[2] Phenomenologically, both trichotillomania and OCD are characterized by compulsive urges and ritualized behaviors and may share similar comorbid disorders.[8]

The pulling behavior in trichotillomania bears some resemblance to compulsions seen in OCD in that it is repetitive and is both anxiety-relieving and excessive.[11]

Despite these compelling similarities, significant phenomenological and functional differences exist between OCD and trichotillomania.[8,12] Comparator studies have indicated that OCD and trichotillomania differ in terms of age at onset (earlier in trichotillomania), gender (more female patients with trichotillomania; equal numbers with OCD), and patterns of comorbidity and interference (OCD having greater interference).[13,14]

Unlike OCD, the hair pulling in trichotillomania rarely occurs in response to an obsessive thought.[11] It is a stereotyped behavior, often occurring without conscious awareness, and more closely resembles tics seen in Tourette's syndrome.

Like OCD with comorbid tics, the motor behavior in trichotillomania is preceded by sensory rather than cognitive phenomena. Trichotillomania may, therefore, be more like *impulsive* OCD rather than classic *compulsive* OCD.[15]

There is considerable evidence to support the key role of the serotonergic system in mediating both impulse dyscontrol and OCD symptoms[16]: (1) Neuroleptics alone appear to be ineffective[17] in treating OCD, although they have been shown to be effective as adjunctive agents.[12] (2) In contrast, tic disorders such as Tourette's syndrome do not respond to serotonin reuptake inhibitors but do respond to neuroleptic medication.[18] (3) The hair pulling behavior of trichotillomania shares many common properties with tic disorders.

Neurobiologic data support trichotillomania as a non-OCD repetitive behavior versus a subtype of OCD, sharing features with various habit and stereotypic movement disorders.[11,19–24] Striatal circuitry has long been thought to mediate OCD, and it has been theorized that OCD

spectrum disorders like trichotillomania are conditions in which a disruption in striatal functioning leads to unwanted repetitive behaviors.[24]

A wide variety of pharmacologic agents have been evaluated in trichotillomania, with mixed results from SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) in open-label studies.[7,25,26] An open-label study of the anticonvulsant topiramate indicated positive results.[27]

The first double-blind crossover comparison in trichotillomania found clomipramine to be superior to desipramine[6]; however, effective treatment of trichotillomania with serotonin reuptake inhibitor medication has not replicated well. Three subsequent controlled trials found no differences between fluoxetine and placebo[28,29] or between fluoxetine and clomipramine.[30] Moreover, in a 22-week study[31] comparing sertraline, behavioral therapy, and combined treatment, patients in all 3 conditions showed improvement in trichotillomania symptoms, with no significant differences between the groups on the primary efficacy measure (although combined treatment was significantly superior on 2 secondary measures of efficacy including the Clinical Global Impressions-Improvement [CGI-I] scale). There has been 1 randomized controlled trial[32] in which the opioid antagonist naltrexone was found to be significantly superior to placebo.

Treating trichotillomania with medications typically used in the treatment of OCD has been largely unsuccessful. When we consider that Tourette's syndrome is also unresponsive to these medications and that, on the basis of clinical phenomenology, trichotillomania may be more like Tourette's syndrome than OCD, we might consider turning to treatments of Tourette's syndrome for the treatment of trichotillomania. Dopaminergic agents (antipsychotics/neuroleptics) are first-line treatments for Tourette's syndrome.[33] This hypothesis is supported by numerous positive case reports using dopaminergic agents, as well as by open-label trials of pimozide,[15] haloperidol,[33] and olanzapine.[34]

Olanzapine is an atypical antipsychotic agent that has potent blockade of serotonin $(5\text{-HT})_2$ and dopamine D_2 receptors. Based on encouraging results in open-label trials with antipsychotic agents, we conducted a 12-week, double-blind, placebo-controlled trial of olanzapine and placebo in the treatment of trichotillomania.

METHOD

Design

Twenty-five outpatients with primary *DSM-IV* trichotillomania were randomly assigned, in double-blind fashion, to flexible-dose olanzapine (2.5–20.0 mg/d) or placebo monotherapy for 12 weeks. Random allocation sequence was implemented using a central telephone. Our statistician (J.O.) generated the allocation sequence, which was sent to a central pharmacy. All study personnel at our site were blinded to group assignment. At the end of 12 weeks, patients entered a 1-week taper phase and then stopped the treatment. The study protocol received full Research Ethics Board approval. Recruitment occurred between August 2001 and December 2005, and follow-up was completed in February 2006.

Sample Size

Power analyses were conducted on the basis of effect-size estimates from Ninan et al[7] and O'Sullivan et al.[35] Ninan et al[7] reported an open trial of venlafaxine in the treatment of trichotillomania using the Massachusetts General Hospital Hair Pulling Scale (MGH)[36] as a primary outcome measure. We expected a mean pretreatment MGH score of 18 (SD, 4.5) and a mean post–olanzapine treatment score of 12 (SD, 4.5), and we expected no effect due to placebo (means and variance were expected to be the same as in the treatment group at baseline). On the basis of these assumptions, we estimated that we required an $n = 12$ per group to achieve power of .90 for a conventional α of .05 (2-tailed).

Participants

Patient recruitment and follow-up are shown in Figure 1, a Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Included in the study were patients aged 18–65 years with primary *DSM-IV* trichotillomania and a Clinical Global Impressions-Severity of Illness (CGI-S)[37] score of 4 or more at baseline. Subjects were recruited through poster advertisement. Exclusion criteria were as follows: any other primary *DSM-IV* disorder; a CGI-S score less than 4 (moderately ill) at baseline; having had an adequate clinical trial of olanzapine in the past; comorbid current OCD, current major depression, or current alcohol or substance abuse; a lifetime history of schizophrenia, bipolar disorder, dementia, or other neurologic disorders.

Patients were asked to discontinue use of all psychotropic medications, including clonidine. Discontinuation period was 5 half-lives (typically 2 weeks for all antidepressants with the exception of fluoxetine, which required 5 weeks; 2 weeks for benzodiazepines; 2 weeks for monoamine oxidase inhibitors). All subjects gave written informed consent.

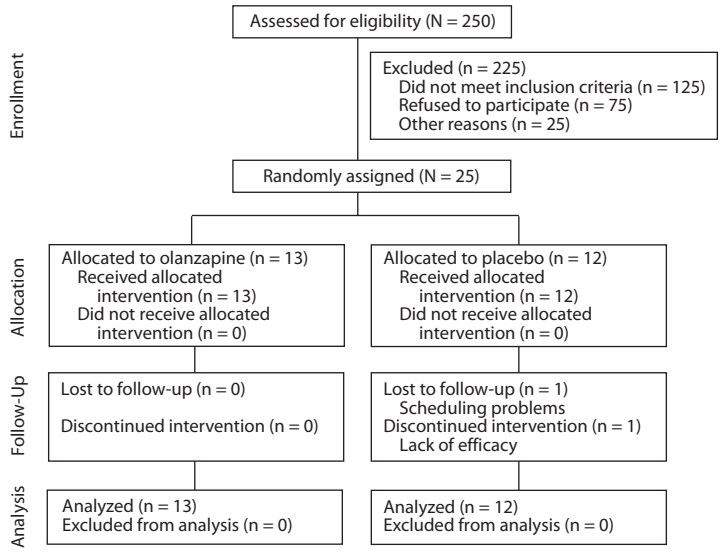
Procedures

Eligible respondents were assessed using the Structured Clinical Interview for *DSM-IV*[38] as well as the Minnesota Trichotillomania Assessment Inventory[39] to confirm the primary diagnosis and the inclusion and exclusion criteria. Subjects were randomly assigned to each condition to receive either flexible doses of olanzapine or placebo. Study participants were assessed at screening, at baseline (week 0), and at each study visit (weeks 2, 4, 6, 8, 10, and 12) by a study psychiatrist.

Dosing

Study medication was administered in flexible doses of 2.5 mg/d for weeks 0 to 3, up to 5.0 mg/d for weeks 4 and 5, up to 10 mg/d for weeks 6 and 7, and up to a maximum dose of 20 mg/d during weeks 8 to 12. The dose was titrated until either response (CGI-I score ≤ 2) or maximum dose

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram of Patient Recruitment and Follow-Up



was achieved. Subjects had to be able to tolerate a minimum of 2.5 mg/d of olanzapine to remain in the study. After week 12, the study medication was tapered over 1 week and then stopped.

Outcome Measures

The primary efficacy measure was the clinician-rated CGI-I[37] scale. Secondary measures of efficacy included change in the clinician-rated CGI-S[37] scale and patient-rated measures of change in the Yale-Brown Obsessive Compulsive Scale for Trichotillomania (TTM-YBOCS),[40] the MGH,[36] and the Quality of Life Enjoyment and Satisfaction Questionnaire,[41] as well as ratings of frequency and severity of hair pulling. Also, changes in scores on the Beck Depression Inventory,[42] the Beck Anxiety Inventory,[43] and the Sheehan Disability Scale[44] were assessed. Remission was defined as complete cessation of hair pulling as reported at study end point.

Additional safety measures involved evaluation for the presence of extrapyramidal side effects at baseline (week 0) and assessment with the Simpson-Angus Scale,[45] the Barnes Akathisia Scale,[46] and the Abnormal Involuntary Movement Scale[47] at weeks 1, 6, and 12. Vital signs and weight were monitored at each study visit. Any additional reports of adverse events were obtained through clinical interview by study psychiatrists. Routine laboratory measures and electrocardiogram were done at baseline.

Data Analysis

The primary efficacy sample was the intent-to-treat sample, which included those subjects who were randomly assigned to treatment, who were able to tolerate olanzapine 2.5 mg/d, and who had at least 1 posttreatment efficacy evaluation.

Change in scores on clinician-report and self-report measures across the duration of the study and across groups were evaluated with a mixed-model analysis of variance. Change from baseline to final visit was treated as a within-subject repeated factor, while the olanzapine/placebo comparison was the between-subject factor. The primary efficacy measure, the clinician-rated CGI-I, was also evaluated as the proportion of improved versus not-improved subjects using a continuity-corrected χ^2 test. Safety and tolerance were evaluated using adverse events and vital-sign measurements. Adverse events were tabulated by treatment, severity, and relation to study drug. Between-group differences in safety and toleration were analyzed with continuity-corrected χ^2 analyses. All safety analyses were performed on the safety sample.

RESULTS

Subjects

The mean ± SD age of the sample was 33.2 ± 9.1 years (range, 18–35 years); the mean ± SD age at trichotillomania onset was 12.1 ± 6.3 years (range, 2–30 years), with a mean ± SD duration of illness of 21.1 ± 10.9 years. Demographic characteristics of the sample are described in Table 1. Sixteen of the 25 subjects (64%) had had no previous treatment. The scalp (19 of 25 patients, 76%), the eyelashes (13 of 25 patients, 52%), and the eyebrows (12 of 25 patients, 48%) were the most common sites from which hair was pulled, and no significant differences were found between the 2 treatment groups. Twenty-three subjects (92%) finished the study. Two subjects dropped out at week 10—one due to lack of effect and the other due to scheduling problems. Both patients were in the placebo group.

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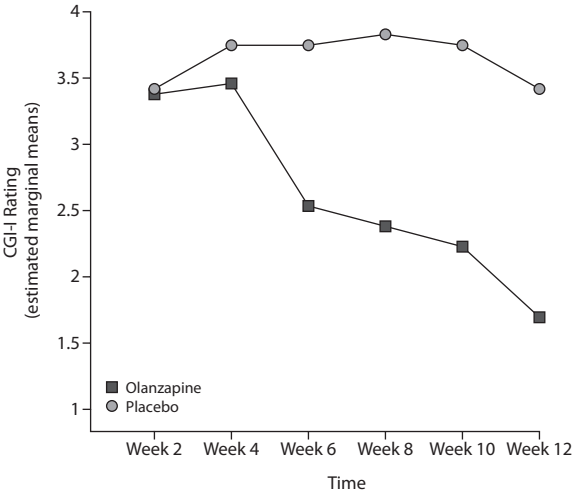
Table 1. Demographic and Clinical Characteristics of the Sample (N = 25)

Variable	Olanzapine (n = 13) Mean (SD)	Olanzapine (n = 13) Range	Placebo (n = 12) Mean (SD)	Placebo (n = 12) Range
Age at presentation, y	33.8 (10.0)	21–55	32.7 (8.4)	18–45
Age at onset, y	10.9 (6.3)	2–30	13.4 (6.2)	4–22
Duration of illness, y	22.9 (12.0)	4–43	19.3 (9.8)	3–34
	n	%	n	%
Gender				
Male	3	23.1	5	41.7
Female	10	76.9	7	58.3
Disorder				
Chronic motor tic disorder	6	46.1	2	16.7
Impulse control disorder not otherwise specified	2	15.4	3	25.0
Social phobia	1	7.7	2	16.7
Panic disorder	0	0.0	1	8.3
Generalized anxiety disorder	0	0.0	1	8.3
Eating disorder not otherwise specified	1	7.7	0	0.0
Past treatment				
SSRI	6	46.1	1	8.3
SNRI	1	7.7	0	0.0
Tricyclic	2	15.4	0	0.0
RIMA	1	7.7	0	0.0
Antipsychotic	1	7.7	0	0.0
Benzodiazepine	1	7.7	1	8.3

Abbreviations: RIMA = reversible inhibitor of monoamine oxidase-A, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Figure 2. Clinical Global Impressions-Improvement (CGI-I) Ratings From Baseline to End Point by Treatment Group[a]



[a]To rule out the possible role of the presence of (1) comorbid chronic motor tics or (2) comorbid impulse control disorder, we included each as a control variable in the analyses. Addition of the control variables did not alter the results, so the results are shown without partialling on control variables. All results are reported with multivariate sphericity assumed; however, all results remained significant after corrections for violations of sphericity.

Efficacy

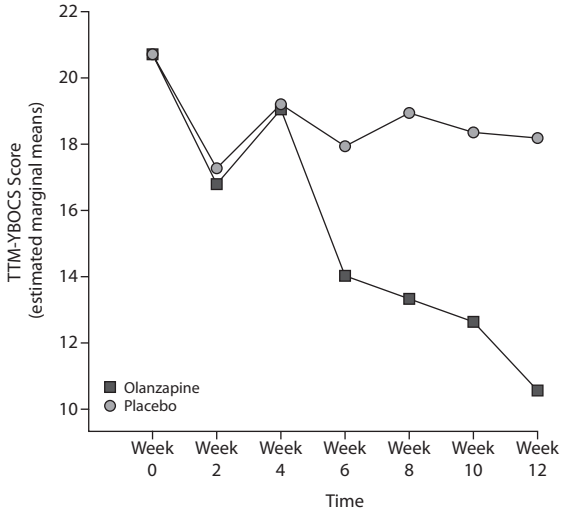
Olanzapine was found to be significantly superior to placebo on the primary efficacy measure, the CGI-I (Figure 2), with significant differences found between the 2 groups as early as week 6. The response rate (a CGI-I score ≤ 2) was 85% (11 of 13) for olanzapine-treated patients compared to 17% (2 of 12) in the placebo group ($F_5 = 3.73$, $P = .001$). Two participants in the olanzapine group (versus none in the placebo group) achieved remission status at study end point (not significant). The change in TTM-YBOCS score was significant for the olanzapine group versus the placebo group (Figure 3) ($F_6 = 3.78$, $P < .01$). The mean ± SD change in TTM-YBOCS score from baseline to end point was 46.0% ± 36.9% for olanzapine and 11.9% ± 19.7% for placebo ($P < .01$). A 35% reduction in TTM-YBOCS score was found in 76.9% of those in the olanzapine group versus 8.3% of those in the placebo group ($P < .001$). The mean change in CGI-S was also significant ($F_7 = 9.99$, $P < .001$) (Table 2). The mean scores for CGI-I, CGI-S, TTM-YBOCS, and MGH are all shown in Table 2. No significant change from baseline to end point was noted for all other secondary outcome measures including the MGH (Figure 4), the Quality of Life Enjoyment and Satisfaction Questionnaire, the Sheehan Disability Scale, and measures of extrapyramidal symptoms (Abnormal Involuntary Movement Scale, Simpson-Angus Scale, and Barnes Akathisia Scale). However, those patients in the olanzapine group had a mean ± SD change in MGH score of 46.8% ± 25.3% versus 17.9% ± 30.4% for those in the placebo group ($P = .02$). No significant relationship was found between end dose of study drug and CGI-I response for either the olanzapine or placebo group.

The most common adverse events were dry mouth (54% for olanzapine [n = 7] versus 0% for placebo; $P < .003$), fatigue (54% for olanzapine [n = 7] versus 0% for placebo; $P < .003$), increased appetite (46% for olanzapine [n = 6] versus 0% for placebo; $P < .007$), headache (38% for olanzapine [n = 5] versus 33% for placebo [n = 4]; not significant), and weight gain (38% for olanzapine [n = 5] versus 8% for placebo [n = 1], not significant). Only 4 of 25 subjects (16%) experienced no adverse events (all 4 were in the placebo group). There was a significant difference in the mean ± SD number of adverse events between groups (4.2 ± 2.0 for olanzapine versus 1.3 ± 1.2 for placebo; $P < .001$). The mean ± SD change in weight from baseline to end point was 4.6 ± 3.1 kg for olanzapine and −0.3 ± 1.4 kg for placebo; $P < .001$. No significant differences were found between the presence of any adverse events and response.

The mean ± SD doses of study medication at end point were 10.8 ± 5.7 mg/d of olanzapine and 19.2 ± 2.9 mg/d of placebo. The mean ± SD time to treatment response was 8.2 ± 3.4 weeks for olanzapine and 0.0 ± 0.0 weeks for placebo. Subjects taking 10 mg/d of olanzapine (n = 6) reported more adverse events (mean ± SD: 5.5 ± 1.0) as compared to those receiving 5 mg/d of olanzapine (n = 4) (mean ± SD: 3.0 ± 1.8) and 20 mg/d of olanzapine (n = 3) (mean ± SD: 3.0 ± 1.4) ($P < .001$).

The end point effect size for olanzapine on the TTM-YBOCS was 1.01 and on the CGI-S was 1.34. The number needed to treat was 1.5.

Figure 3. Change in the Yale-Brown Obsessive Compulsive Scale for Trichotillomania (TTM-YBOCS) Scores From Baseline to End Point by Treatment Group[a]



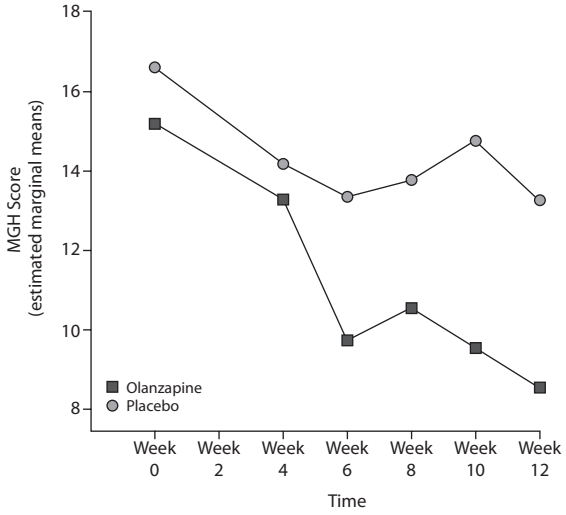
[a]To rule out the possible role of the presence of (1) comorbid chronic motor tics or (2) comorbid impulse control disorder, we included each as a control variable in the analyses. Addition of the control variables did not alter the results, so the results are shown without partialling on control variables. All results are reported with multivariate sphericity assumed; however, all results remained significant after corrections for violations of sphericity.

Table 2. Outcome Measures From Baseline to Week 12 by Treatment Group

Week	CGI-I, Mean (SD)	CGI-S, Mean (SD)	TTM-YBOCS, Mean (SD)	MGH, Mean (SD)
Week 0 (baseline)				
Olanzapine	NA	5.08 (0.76)	20.70 (4.29)	15.46 (4.46)
Placebo	NA	5.00 (0.74)	20.67 (3.72)	16.58 (5.07)
Week 2				
Olanzapine	3.38 (0.96)	4.69 (0.75)	16.77 (5.21)	NA
Placebo	3.41 (1.31)	4.50 (0.90)	17.25 (5.19)	NA
Week 4				
Olanzapine	3.46 (0.97)	4.77 (0.83)	19.00 (5.54)	13.07 (4.07)
Placebo	3.75 (1.05)	4.75 (0.75)	19.17 (5.76)	14.17 (5.78)
Week 6				
Olanzapine	2.54 (0.78)	4.38 (0.77)	14.00 (4.34)	9.50 (3.60)
Placebo	3.75 (0.75)	4.83 (0.71)	17.91 (3.20)	13.33 (3.50)
Week 8				
Olanzapine	2.38 (1.39)	4.15 (1.07)	13.30 (6.61)	10.42 (6.71)
Placebo	3.83 (0.83)	4.75 (0.62)	18.92 (4.21)	13.75 (3.65)
Week 10				
Olanzapine	2.23 (1.30)	3.77 (1.30)	12.61 (6.76)	8.77 (5.67)
Placebo	3.75 (1.22)	5.00 (0.74)	18.33 (5.88)	14.75 (5.12)
Week 12 (endpoint)				
Olanzapine	1.69 (1.18)	3.15 (0.90)	10.54 (6.74)	8.38 (4.23)
Placebo	3.41 (0.90)	4.83 (0.71)	18.17 (5.27)	13.25 (5.72)
Analysis				
F statistic	3.73	9.99	3.78	1.23
df	5	7	5	5
P value	.001	<.001	<.01	.30

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, MGH = Massachusetts General Hospital Hair Pulling Scale, NA = not applicable, TTM-YBOCS = Yale-Brown Obsessive Compulsive Scale for Trichotillomania.

Figure 4. Change in the Massachusetts General Hospital Hair Pulling Scale (MGH) Scores From Baseline to End Point by Treatment Group[a]



[a]To rule out the possible role of the presence of (1) comorbid chronic motor tics or (2) comorbid impulse control disorder, we included each as a control variable in the analyses. Addition of the control variables did not alter the results, so the results are shown without partialling on control variables. All results are reported with multivariate sphericity assumed; however, all results remained significant after corrections for violations of sphericity.

A logistic regression analysis was conducted to examine predictors of clinical response. The dichotomous dependent variable was responder status (in which *responder* was defined as a CGI-I score ≤2). Candidate predictor variables included gender, marital status, years of education, employment status, age, and years with the disorder. Two of the variables (years with the disorder and age at baseline) were highly correlated ($r = 0.82$) and together were somewhat suggestive that a lower age at baseline predicted higher likelihood of nonresponse. No other predictors were significantly associated with clinical response after taking into account the treatment group to which the patient was assigned. These findings are very speculative, however, as they are based on 25 cases, but they may be useful to track for future investigations.

DISCUSSION

The main finding of this study was the significant superiority of olanzapine compared to placebo in the treatment of primary *DSM-IV* trichotillomania. In the context of the trichotillomania treatment literature, this finding may be an important one as there have been few agents that have demonstrated efficacy in a controlled trial—and none demonstrating comparable response (85.0% according to CGI-I; 76.9% according to TTM-YBOCS).

Although there was not a significant difference between the 2 groups on the MGH ($F_5 = 1.23$, $P = .30$; Table 2), if we examine the slope of the placebo group (Figure 4), there is a trend toward some initial improvement, then a decline to baseline with the final time point being deviant. If the study

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had been longer, a statistically significant finding would most likely have been observed as it has been well documented that, although self-monitoring improves habit problems, this effect is not enduring. Moreover, the mean drop in MGH was significant for olanzapine. The differences between the 2 groups in terms of impairment (measured by the Sheehan Disability Scale) were not significant; however, this finding was most likely a factor of time and power ($F_1 = 1.44$). With a larger sample, the effect size would quite likely be clinically significant as the effect was in the predicted direction and the scores of the 2 groups were well separated at end point. In addition, the lack of change on the Sheehan Disability Scale and the Quality of Life Enjoyment and Satisfaction Questionnaire may not be surprising as the functional impairment caused by trichotillomania is much less than that attributed to many other anxiety and psychiatric disorders. In addition, this was a 12-week study, and these instruments may not be as sensitive to change in a short-term study with this patient population.

The mean dose of olanzapine in this study was 10.8 mg/d. In flexible-dose studies using schizophrenic or bipolar populations, mean doses range from 8.6 mg/d to 16.2 mg/d.[48–50] Within these populations, a relationship between dose and adverse events has been found, with higher doses resulting in greater prevalence of certain adverse events.[51] In our study, 10 mg/d of olanzapine resulted in the most adverse events; however, twice as many people were at this dose level as compared to 5 mg/d or 20 mg/d. This dose-related effect needs to be further evaluated in a fixed-dose study. There is some suggestion that the adverse events attributed to olanzapine are reversible[52] when treatment is discontinued; however, the long-term adverse effects of olanzapine in trichotillomania are unknown.

The primary limitation of this study is the small sample size. Nevertheless, it is the largest randomized controlled trial in trichotillomania in the psychiatric literature. Although we believe the efficacy of olanzapine seen in this study is related to the dopaminergic properties of this agent, one could not rule out the possibility that the potential benefits of olanzapine may have been due to the 5-HT_{2A} blockade associated with atypicals. Although we didn't find any significant metabolic effects with olanzapine in this study, metabolic effects have been found with the use of atypicals and may be a potential limitation in the long-term use of olanzapine for the treatment of trichotillomania. There was a significantly greater proportion of dry mouth, fatigue, and increased appetite in the olanzapine group, although no participant withdrew as a result of an adverse event. There were no significant associations found between these adverse events and response, nor between the presence of an adverse event and response. The weight gain associated with olanzapine reported in this study and throughout the literature is a significant issue and may pose a limiting factor for treatment with this agent, especially since the weight gain appears to be significant in both short-term and long-term studies in schizophrenic and bipolar patient populations.[49,53] However, it seems likely that improvement in trichotillomania symptoms would occur with other atypical antipsychotic agents, and the use of another agent with a more favorable metabolic profile may be an alternative treatment option.

As with most clinical trials, our participants were recruited through advertising rather than from our clinic patient population. This method of recruiting may potentially limit the generalizability of the findings. Although this bias has not been examined in trichotillomania patients, a report by Rapaport et al[54] compared symptomatic volunteers and clinical anxiety disorder patients and found no differences in functional disability, although the volunteers had more presenting symptoms than did the clinical patients. We did not use independent evaluators in this study. This may have posed a potential limitation as the side-effect profile of olanzapine was already known by treating physicians and may have resulted in a rating bias. However, given that patients' MGH scores also improved, any potential bias caused by this issue was most likely small.

There were more individuals in the olanzapine group with comorbid tics; however, no differences were found in response rates between those who had comorbid tics and those who did not ($\chi^2 = 0.52$, $P = .47$). Furthermore, improvements were evident on measures of hair pulling as well as on global clinical improvement (CGI-I) in individuals with and without comorbid tics.

In addition, participants with a primary *DSM-IV* disorder other than trichotillomania were excluded from the study. Although this may be a limiting factor, comorbid *DSM-IV* anxiety conditions were permitted (a typical clinical presentation of trichotillomania) as long as they were not primary. Given the significant degree of comorbidity between trichotillomania and major depressive disorder,[2] the exclusion of major depressive disorder may limit the generalizability of the findings. However, as olanzapine has been shown to have antidepressant properties when used as an adjunctive agent in bipolar disorder and treatment-refractory depression,[55,56] the exclusion of major depressive disorder comorbidity eliminates another potentially confounding factor.

Although there was a higher incidence of comorbid anxiety disorders in the placebo group (n = 3) than in the olanzapine group (n = 1), no significant relationship was found between comorbid anxiety disorders and response, nor between the presence of any comorbid disorder and response.

When we compare the characteristics of the olanzapine group versus the placebo group, the groups are consistent in terms of mean age. The olanzapine group had a slightly higher female to male ratio as well as a younger mean age at onset and longer duration of illness. In the olanzapine group, 7 patients had had previous treatment for trichotillomania compared with 2 patients in the placebo group ($\chi^2 = 3.74$, $P = .05$). Therefore, even though the olanzapine group had a higher proportion of previous treatment nonresponders, the treatment response to olanzapine was not adversely affected.

CONCLUSION

Olanzapine seems to be a safe and effective short-term treatment for primary *DSM-IV* trichotillomania. Unlike OCD, trichotillomania appears to respond to antipsychotic monotherapy. This study lends further support to the idea of trichotillomania as a non-OCD, unwanted, repetitive behavior versus being a type of OCD, having more features in common with various habit and stereotypic movement disorders than with OCD. Neurobiologic and treatment data seem to support this relationship. When the neuroimaging data of trichotillomania is compared to that of OCD, there appear to be more differences than similarities. Neuroimaging studies using structural magnetic resonance imaging have shown little overlap between OCD and trichotillomania. For example, striatal volume is smaller in trichotillomania (and in Tourette's syndrome)[20] but not in OCD, in which abnormalities in the symmetry of striatal structures has been found.[57] Prefrontal cortex volume is larger in trichotillomania (and in Tourette's syndrome)[20] but smaller in OCD.[58] In terms of functional neuroimaging, examination of regional cerebral blood flow using positron emission tomography has shown increased activity in the striatum and orbitofrontal cortex in OCD,[59] whereas blood-oxygen level–dependent functional magnetic resonance imaging has shown increased activation in the sensory motor areas and superior parietal cortex in trichotillomania and Tourette's syndrome.[60] Treatment studies of trichotillomania using first-line OCD medications have not yielded the positive results found in OCD.[6,28,29,31] This study needs to be replicated in a larger, controlled population and with other antipsychotic agents.

Drug names: clomipramine (Anafranil and others), clonidine (Catapres, Duraclon, and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), naltrexone (Vivitrol, ReVia, and others), olanzapine (Zyprexa), pimozide (Orap), sertraline (Zoloft and others), topiramate (Topamax and others).

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