N-Acetylcysteine, a Glutamate Modulator, in the Treatment of Trichotillomania

A Double-blind, Placebo-Controlled Study

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Context: Trichotillomania is characterized by repetitive hair pulling that causes noticeable hair loss. Data on the pharmacologic treatment of trichotillomania are limited to conflicting studies of serotonergic medications. N-acetylcysteine, an amino acid, seems to restore the extracellular glutamate concentration in the nucleus accumbens and, therefore, offers promise in the reduction of compulsive behavior.

Objective: To determine the efficacy and tolerability of N-acetylcysteine in adults with trichotillomania.

Design: Twelve-week, double-blind, placebo-controlled trial.

Setting: Ambulatory care center.

Patients: Fifty individuals with trichotillomania (45 women and 5 men; mean [SD] age, 34.3 [12.1] years).

Interventions: N-acetylcysteine (dosing range, 1200-2400 mg/d) or placebo was administered for 12 weeks.

Main Outcome Measures: Patients were assessed using the Massachusetts General Hospital Hair Pulling Scale, the Clinical Global Impression scale, the Psychiatric Institute Trichotillomania Scale, and measures of depression, anxiety, and psychosocial functioning. Outcomes were examined using analysis of variance modeling analyses and linear regression in an intention-to-treat population.

Results: Patients assigned to receive N-acetylcysteine had significantly greater reductions in hair-pulling symptoms as measured using the Massachusetts General Hospital Hair Pulling Scale ($P < .001$) and the Psychiatric Institute Trichotillomania Scale ($P = .001$). Fifty-six percent of patients "much or very much improved" with N-acetylcysteine use compared with 16% taking placebo ($P = .003$). Significant improvement was initially noted after 9 weeks of treatment.

Conclusions: This study, the first to our knowledge that examines the efficacy of a glutamatergic agent in the treatment of trichotillomania, found that N-acetylcysteine demonstrated statistically significant reductions in trichotillomania symptoms. No adverse events occurred in the N-acetylcysteine group, and N-acetylcysteine was well tolerated. Pharmacologic modulation of the glutamate system may prove to be useful in the control of a range of compulsive behaviors.

Trial Registration: http://www.clinicaltrials.gov Identifier: NCT00354770.

TRICHOTILLOMANIA IS A DISabling, underrecognized condition in which individuals repeatedly pull out hair, which leads to noticeable hair loss. Trichotillomania is characterized by the following diagnostic criteria: the recurrent pulling out of one's hair, which results in noticeable hair loss; an increasing sense of tension immediately before pulling out the hair or when attempting to resist the behavior; and pleasure, gratification, or relief when pulling out hair.[1] Psychosocial problems are common in individuals with trichotillomania and include significantly reduced quality of life, reduced work productivity, and impaired social functioning.[2,3]

Relatively little is known about the prevalence of trichotillomania in the general population. Clinically significant hair pulling that meets the diagnostic criteria for trichotillomania has been found in 0.6% to 3.9% of college students surveyed.[4,5] Other studies examining the rates of trichotillomania in treatment samples have found lifetime rates of 4.4% in adult psychiatric inpatients (sample size=204)[6] and 4.6% in patients with obsessive-compulsive disorder (sample size=153).[7]

Although trichotillomania has been described for almost 2 centuries,[8] it remains

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a poorly understood disorder with limited data regarding pathogenesis and treatment.[9] Currently, there is no Food and Drug Administration–approved treatment for trichotillomania, despite almost 2 decades of research. In fact, there have been only 6 small (sample sizes=13-43) placebo-controlled trials of pharmacotherapy published for the treatment of trichotillomania.[9] Four of these studies examined a selective serotonin reuptake inhibitor, and 2 investigated clomipramine hydrochloride. A recent meta-analysis[10] demonstrated that although clomipramine has moderate efficacy compared with placebo (effect size, –0.68; 95% confidence interval, –1.28 to –0.07), there is no evidence to suggest any benefit for selective serotonin reuptake inhibitors (SSRIs) (effect size, –0.02; 95% confidence interval, –0.32 to 0.35). Even in the case of clomipramine, however, there is little evidence that initial benefits are maintained.[11] Given the lack of clearly effective pharmacologic treatments for trichotillomania, additional treatment options are needed.

Glutamatergic dysfunction has been implicated in the pathogenesis of obsessive-compulsive disorder,[12,13] a disorder with phenomenologic and possible neurobiological links to trichotillomania.[14-17] Clinical studies[18-20] support the possible efficacy of glutamatergic modulators, such as N-acetylcysteine, in the treatment of repetitive or compulsive disorders. N-acetylcysteine is a hepatoprotective antioxidant that is converted to cystine, a substrate for the glutamate-cystine antiporter. This antiporter allows for the uptake of cystine, which causes the reverse transport of glutamate into the extracellular space, which stimulates inhibitory metabotropic glutamate receptors and, thereby, reduces synaptic release of glutamate.[13,18,21-24] The restoration of the extracellular glutamate concentration in the nucleus accumbens seems to block reinstitution of compulsive behaviors.[21,25] Pharmacotherapies that target the prefrontal glutamatergic drive to the nucleus accumbens,[25] such as N-acetylcysteine, may, therefore, correct the underlying pathophysiologic abnormalities and symptoms of trichotillomania. Based on these data, we conducted a placebo-controlled, double-blind study to examine the tolerability and efficacy of N-acetylcysteine in the treatment of trichotillomania. We hypothesized that the use of N-acetylcysteine would reduce compulsive hair-pulling behavior in individuals with trichotillomania.

METHODS

PATIENTS

Men and women aged 18 to 65 years with a primary DSM-IV[26] diagnosis of trichotillomania were recruited via newspaper advertisements and referrals for medication treatment. All the patients met the DSM-IV criteria for current trichotillomania using the physician-administered Trichotillomania Diagnostic Interview.[27] Because 17% of individuals with trichotillomania do not meet the DSM-IV criteria of either tension before or relief or gratification after pulling hair,[28] this criterion was not required for study inclusion (46 patients, however, met the full DSM-IV criteria for trichotillomania). The participation of women required a negative β–human chorionic gonadotropin pregnancy test result and the stable use of a medically accepted form of contraception.

The exclusion criteria included (1) unstable medical illness or clinically significant abnormalities on laboratory tests or physical examination at the screening visit; (2) a history of seizures; (3) myocardial infarction within 6 months; (4) current pregnancy or lactation or inadequate contraception in women of childbearing potential; (5) any reported thoughts of suicide; (6) a lifetime history of bipolar disorder type I or II, dementia, or schizophrenia or any other psychotic disorder according to DSM-IV criteria; (7) current (past 3 months) DSM-IV–designated substance abuse or dependence; (8) previous treatment with N-acetylcysteine; and (9) a diagnosis of asthma (owing to the potential of N-acetylcysteine to worsen asthma).

Patients who were currently taking psychotropic medications were allowed into the study as long as the dose of medication had been stable for 3 months before study inclusion and there were no plans to modify the dose during the study. Similarly, patients who were attending individual or group psychotherapy were allowed to participate if attendance had been ongoing weekly for at least 6 months before study entry. Patients who had changed doses of medication or started therapy, based on self-report, were discontinued from the study (changes in treatment were assessed at each study visit, and no one was withdrawn for this reason).

Of 77 individuals screened for the study, 50 with trichotillomania (45 women and 5 men; mean [SD] age, 34.3 [12.1] years) were randomized to receive N-acetylcysteine or placebo. Twenty-seven individuals did not meet the inclusion and exclusion criteria: 13 reported a current substance use disorder, 6 reported symptoms consistent with a lifetime bipolar disorder, 5 had severe asthma, and 3 felt unable to comply with the study schedule.

The 50 randomized patients as a whole reported a mean (SD) age at trichotillomania onset of 12.1 (5.0) years (range, 3-27 years). Patients spent a mean (SD) of 64.9 (59.1) minutes each day pulling hair. Although many patients had multiple triggers, the most common triggers of actual pulling were the feel of the hair (eg, coarse, kinky, or out-of-place hairs) (60%; n=30), stress (34%; n=17), and the sight of a hair (22%; n=11). Most patients (n=37; 74%) pulled from multiple sites: 33 (66%) pulled from their heads, 30 (60%) from their eyebrows, 25 (50%) from their eyelashes, and 7 (14%) from their pubic area. Twelve patients (24%) pulled without complete conscious awareness. Ten patients (20%) reported ingesting at least part of the hair (ie, root or shaft) after pulling. Seven patients (14%) reported pulling the hair of someone else in addition to their own. Of the 50 patients, 31 (62%) had never sought outpatient mental health treatment for hair pulling.

Although individuals with current bipolar, psychotic, and substance use disorders were excluded, 30 enrolled patients (60%) reported at least 1 clinically important current comorbid disorder: 14 (28%) reported symptoms consistent with major depressive disorder, 14 (28%) had an anxiety disorder (eg, generalized anxiety disorder, posttraumatic stress disorder, obsessive-compulsive disorder, or anxiety disorder not otherwise specified), 18 (36%) had another impulse control disorder (most commonly pathologic skin picking and compulsive nail biting), and 1 (2%) had an eating disorder (ie, bulimia nervosa). Rates of comorbid disorders did not differ between treatment groups, and no particular comorbid disorder was associated with treatment response.

Of the 50 patients, 4 (8%) had ongoing psychotherapy and 28 (56%) were taking a psychotropic medication. Of the 4 patients undergoing psychotherapy, all had been with the same therapist for at least 1 year, and no one was receiving cognitive behavior therapy (when efficacy analyses were performed without these 4 patients, the results were the same). Of the 28 patients taking medication, all had been taking stable doses for at least 6 months: 18 were taking a selective serotonin reuptake inhibitor, 8 were taking a serotonin-norepinephrine re-

uptake inhibitor, and 2 were taking a stimulant. Rates of psychotropic medication use did not differ between the treatment groups (64% of the placebo group and 48% of the N-acetylcysteine group; $\chi^2_1 = 1.299$; $P = .25$), and no particular medication was associated with treatment response.

The institutional review board of the University of Minnesota approved the study and the informed consent. One of 2 investigators (J.E.G. or S.W.K.) discussed potential risks of the study, as well as alternative treatments, with the patients. After having received a complete description of the study, patients provided written informed consent. This study was performed in accordance with the Declaration of Helsinki. Data were collected between September 1, 2006, and August 1, 2008.

STUDY DESIGN

After screening, eligible patients were assigned to 12 weeks of double-blind N-acetylcysteine or placebo therapy. The investigational pharmacy of the University of Minnesota randomized all the patients (in block sizes of 8 using computer-generated randomization with no clinical information) to either N-acetylcysteine or placebo in a 1:1 manner. All eligible study participants were first given N-acetylcysteine, 1200 mg/d, or matching placebo for 6 weeks. At week 6, the dose was increased to 2400 mg/d (or the same number of matching placebo pills) for the remaining 6 weeks of the study. Dose range selection was based on safety and efficacy data from studies using N-acetylcysteine in human immunodeficiency virus, cocaine dependence, and other impulse control disorders, such as pathologic gambling.[29-31] At week 6, the dose was increased unless clinical improvement (ie, cessation of all hair pulling for the entire 3-week period as assessed by the investigator) was attained at a lower dose. Twenty-two patients (88%) in the placebo group received the dose increase, whereas 18 (72%) assigned to N-acetylcysteine received a dose increase ($\chi^2_1 = 2.000$; $P = .16$). Given the lack of difference between groups in terms of dose increase, change in dose would be unlikely to have affected the masking. Patients who were not compliant with their use of study medication (ie, who failed to take medication for ≥ 3 consecutive days) were discontinued from the study. Patients were asked at each visit about the number of doses missed per week. Forty-four patients reported never missing a dose, and 6 reported missing at most 1 or 2 doses each month.

SCREENING ASSESSMENTS

Patients were evaluated at study entry using the Trichotillomania Diagnostic Interview, a reliable and valid diagnostic instrument that uses the *DSM-IV* criteria for trichotillomania.[27] Demographics and clinical features of trichotillomania were assessed by the use of a semistructured interview. The ethnicity of patients in the study was defined by self-report and was included to learn more about this variable in trichotillomania. Psychiatric comorbidity was assessed using the *Structured Clinical Interview for* DSM-IV.[32] Medical history, physical examination, and routine laboratory testing were performed. Patients reported the severity of trichotillomania symptoms using the self-rated Massachusetts General Hospital Hair Pulling Scale (MGH-HPS).[33] Investigators assessed trichotillomania symptoms by the use of the physician-administered Psychiatric Institute Trichotillomania Scale (PITS).[34] Anxiety symptom severity was rated using the Hamilton Anxiety Rating Scale (HAM-A).[35] Depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HAM-D).[36] Psychosocial functioning was evaluated using the self-report version of the Sheehan Disability Scale (SDS),[37] and quality of life was evaluated using the Quality of Life Inventory.[38]

EFFICACY ASSESSMENTS

Patients were seen every 3 weeks for 12 weeks. Whichever investigator (J.E.G. or S.W.K.) did not see a particular patient at baseline conducted the progress evaluations for that patient. The primary outcome measure was the MGH-HPS.[33] The MGH-HPS is a 7-item self-report scale that rates urges to pull hair, actual amount of pulling, perceived control over the behavior, and distress associated with hair pulling in the past 7 days on a severity scale from 0 to 4 for each item (total scores range from 0 to 28, with higher scores reflecting greater illness severity). The MGH-HPS has demonstrated excellent test-retest reliability, convergent and divergent validity, and sensitivity to change.[39] Analysis of the MGH-HPS has demonstrated 2 separate factors, with acceptable reliability for both: "severity" and "resistance and control."[40] Separate treatment effects for these 2 factors were also analyzed.

Secondary measures used at each study visit included the following:

1. *The PITS.*[34] This is a 6-item physician-administered scale that rates hair-pulling symptoms during the past week. The items assess number of hair-pulling sites, time spent pulling and thinking about pulling, resistance to hair-pulling urges, distress, and interference with daily activities. Items are rated from 0 to 7, with higher scores a reflection of greater severity and total scores ranging from 0 to 42. Although the psychometric properties of the PITS have not been well established,[41,42] as 1 of the few physician-rated instruments for trichotillomania, it has shown strong correlation with the MGH-HPS ($r = 0.63$).[39]

2. *The Clinical Global Impression (CGI) scale.*[44] This scale consists of a reliable and valid 7-item Likert scale used to assess the severity and improvement of clinical symptoms. The CGI severity scale was used at each visit and ranges from 1 ("not ill at all") to 7 ("among the most extremely ill"). The CGI improvement scale was used at each follow-up visit and ranges from 1 ("very much improved") to 7 ("very much worse"). The CGI scale was used to refer specifically to trichotillomania symptoms and not to the overall psychopathologic condition.

3. *The SDS.*[37] This reliable, valid 3-item self-report scale assesses functioning in 3 areas of life: work, social or leisure activities, and home and family life. Scores on the SDS range from 0 to 30.

4. A secondary measure used only at baseline and the study end point was the *Quality of Life Inventory.*[37] This inventory is a valid and reliable 16-item self-administered rating scale that assesses life domains such as health, work, recreation, friendships, love relationships, home, self-esteem, and standard of living.

5. *The HAM-A and the HAM-D.* The HAM-A[35] is a reliable and valid physician-administered 14-item scale that provides a total measure of overall anxiety. The HAM-D[36] is a valid and reliable 17-item physician-administered rating scale that assesses the severity of depressive symptoms.

SAFETY ASSESSMENTS

Safety assessments at each visit included evaluations of sitting blood pressure, heart rate, and weight. Adverse effects were documented and included time of onset and resolution, severity, action taken, and outcome. Common adverse effects of N-acetylcysteine therapy include headache, pruritus, flatulence, increased blood pressure, and fatigue. The investigator recorded the use of concomitant medications in terms of daily dosage, start and stop dates, and reason for use.

DATA ANALYSIS

Demographic and baseline visit characteristics of the N-acetylcysteine and placebo groups were compared using χ^2 and t tests to determine whether group differences existed at ran-

Table 1. Baseline Comparison of Patients With Trichotillomania Assigned to Receive *N*-Acetylcysteine or Placebo

	Patients, No. (%)				
	Placebo Group (n=25)	*N*-Acetylcysteine Group (n=25)	Test[a]	df	P Value
Variable					
Age, mean (SD) [range], y	35.8 (13.6) [18-59]	32.7 (10.5) [18-55]	−0.883	45.073	.38
Female sex, No. (%)	21 (84)	24 (96)	f	NA	.35
White race, No. (%)	24 (96)	23 (92)	f	NA	>.99
Married, No. (%)	9 (36)	10 (40)	f	NA	.88
Age at onset, mean (SD) [range], y	15.1 (8.5) [5-48]	11.2 (4.7) [2-22]	−2.042	48	.047
Any psychiatric comorbidity, No. (%)	18 (72)	12 (48)	3.000c	1	.08
MGH-HPS total score, mean (SD) [range]	16.7 (5.28) [8-26]	17.6 (4.64) [4-26]	−0.537	48	.59
MGH-HPS factor 1 scale score, mean (SD)	9.04 (3.26)	10.04 (2.84)	−1.157	48	.25
MGH-HPS factor 2 scale score, mean (SD)	7.68 (2.45)	7.52 (2.08)	0.249	48	.80
PITS total score, mean (SD) [range]	23.0 (4.79) [16-33]	21.2 (4.66) [9-33]	1.318	48	.19
CGI severity scale score, mean (SD) [range]	4.72 (0.84) [4-7]	4.28 (0.74) [3-6]	−1.965	48	.06

Abbreviations: c, χ^2 test; CGI, Clinical Global Impression; f, Fisher exact test; MGH-HPS, Massachusetts General Hospital Hair Pulling Scale; MGH-HPS factor 1 scale, severity scale; MGH-HPS factor 2 scale, resistance and control scale; NA, not applicable; PITS, Psychiatric Institute Trichotillomania Scale.

[a] *t* test unless otherwise indicated.

domization. Differences in response between the placebo and *N*-acetylcysteine groups were adjusted for baseline disparities by use of the baseline score as a covariate.

Primary and secondary measures were examined using analysis of variance modeling analyses (UNIANOVA, SPSS for Windows version 15.0; SPSS Inc, Chicago, Illinois). The baseline value of the measure being analyzed was used as a covariate. The difference in the overall level of posttreatment values, the main effect for treatment, was the test of primary interest. Analyses were performed on all available data by the use of an intention-to-treat population (last observation carried forward). All patients who returned for at least 1 postrandomization visit were included in the intention-to-treat population. Because 7 dependent variables were being examined, a Bonferroni correction was used; tests were 2-tailed, and $\alpha = .007$ ($0.05/7=.007$) was used to determine statistical significance.

A retrospective power analysis was performed using a bootstrap approach.[43] A total of 10 000 repeated sampling iterations were performed, and significance at $P=.007$ was achieved in 99.9% of the 2-level active-placebo dichotomy using the primary outcome measure (the MGH-HPS). These results indicate that the significant findings reported are not likely to be based on chance.

Effect sizes were also calculated using the Cohen effect size index *d*. A *d* of 0.2 is considered a small effect size, 0.5 is medium, and 0.8 is large. Partial eta squared (η^2), which is the proportion of the effect + error variance that is attributable to the effect, was calculated. Interpretation of η^2 is that greater than 0.2 is a large effect size, greater than 0.1 is a medium effect size, and greater than 0.05 is a small effect size.

Clinically significant change was determined using the approach developed by Jacobson and Truax.[45] The CGI severity scale was used to assess clinically significant change after treatment. For someone to have a clinically significant change, his or her final CGI severity score had to be less than the cutoff score, and his or her change from baseline had to be greater than the reliable change index.

RESULTS

PATIENT CHARACTERISTICS

Demographics and clinical characteristics of the patients at baseline are given in **Table 1** and **Table 2**. There were no statistically significant imbalances regarding demographics or baseline trichotillomania symptoms between treatment groups. Baseline trichotillomania scores on both the MGH-HPS and the PITS were consistent with severity scores seen in other studies of trichotillomania.[46] In addition, overall baseline psychosocial dysfunction, according to the SDS, was mild, and quality of life was assessed in the "low average" range, both of which are consistent with assessments made in other studies.[3] Although some of the baseline scores on the MGH-HPS were in the low range at baseline, the low scorers did not experience a floor effect for symptom change during treatment. In the placebo group, only 2 patients had a minimum score on a single item, and at the end point neither of these patients had a minimum score on any item. In the *N*-acetylcysteine group, only 1 patient had a minimum item score, and at the end point, this patient also had a minimum score on each of 4 items.

Figure 1 shows the patient disposition throughout the study. Twenty-two of 25 patients (88%) assigned to receive *N*-acetylcysteine and 22 of 25 patients (88%) assigned to receive placebo completed the 12-week trial. There were no statistically significant pretreatment differences between completers and noncompleters on any measures. The rate of study completion did not differ between treatment groups. Of the 6 patients who did not complete the study, 1 withdrew for health concerns unrelated to the study and 5 withdrew because of an inability to comply with the study schedule. Reasons for study withdrawal did not significantly differ between groups.

EFFICACY RESULTS

Significantly better results on the primary efficacy variable, the MGH-HPS total score, were observed for patients assigned to receive *N*-acetylcysteine by the study end point ($F_{1,47}=32.152$; $P<.001$) (Table 2). A significant treatment effect was first detected after 9 weeks of active medication use ($P=.002$) (**Figure 2**). In terms of the 2 factors of the MGH-HPS, those assigned to the

Table 2. Treatment Responses of Patients With Trichotillomania Assigned to Receive Placebo or *N*-Acetylcysteine (Intention-to-Treat)

| | Value, Mean (SD) [Range] | | | | | | | |
| | Baseline | | End Point | | | | | |
Variable	Placebo Group (n=25)	*N*-Acetylcysteine Group (n=25)	Placebo Group (n=25)	*N*-Acetylcysteine Group (n=25)	F Test$_{1,47}$ [a]	P Value	Effect Size[b] (95% CI)	Partial η^{2}[c]
MGH-HPS total score	16.7 (5.28) [8-26]	17.6 (4.64) [4-26]	16.0 (4.90) [6-24]	10.4 (5.55) [0-24]	32.152	<.001	−1.19 (−1.77 to −0.57)	0.406
MGH-HPS factor 1 scale score	9.04 (3.259) [4-15]	10.04 (2.835) [3-15]	8.32 (2.854) [3-13]	5.80 (3.055) [0-14]	18.245	<.001	−1.03 (−1.61 to −0.43)	0.280
MGH-HPS factor 2 scale score	7.68 (2.445) [3-11]	7.52 (2.084) [1-12]	7.68 (2.322) [3-12]	4.60 (2.754) [0-10]	37.067	<.001	−1.16 (−1.74 to −0.54)	0.441
PITS total score	23.0 (4.79) [16-33]	21.2 (4.66) [9-33]	18.7 (5.41) [5-32]	11.8 (7.61) [0-33]	12.03	.001	−0.84 (−1.41 to −0.25)	0.204
SDS total score	10.7 (6.24) [0-25]	9.0 (6.6) [0-25]	8.36 (4.94) [0-20]	5.60 (5.23) [0-18]	2.683	.11	−0.42 (−0.97 to 0.15)	0.054
CGI severity scale score	4.72 (.84) [4-7]	4.28 (.747) [3-6]	4.20 (1.08) [1-6]	2.96 (1.379) [1-6]	5.118	.03	−1.30 (−1.88 to −0.67)	0.098
HAM-D score	3.68 (2.51) [0-9]	3.68 (3.90) [0-13]	3.32 (3.68) [0-15]	2.36 (2.98) [0-10]	0.915	.34	−0.21 (−0.76 to 0.35)	0.019
HAM-A score	3.72 (2.28) [0-9]	3.40 (3.64) [0-13]	3.20 (3.27) [0-12]	2.32 (2.94) [0-8]	1.354	.25	−0.11 (−0.66 to 0.45)	0.028
Quality of Life Inventory score	42.56 (13.70) [15-68]	45.16 (12.08) [16-64]	45.12 (15.84) [0-71]	50.24 (11.12) [28-69]	1.337	.25	0.24 (−0.32 to 0.079)	0.028

Abbreviations: CGI, Clinical Global Impression; CI, confidence interval; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; MGH-HPS, Massachusetts General Hospital Hair Pulling Scale; MGH-HPS factor 1 scale, severity scale; MGH-HPS factor 2 scale, resistance and control scale; PITS, Psychiatric Institute Trichotillomania Scale; SDS, Sheehan Disability Scale.

[a] Analysis of variance, with the baseline value as a covariate.
[b] Cohen effect size based on adjusted differences in response between the placebo and *N*-acetylcysteine groups (adjusted for baseline level).
[c] Partial η^{2} is the proportion of the effect + error variance that is attributable to the effect.
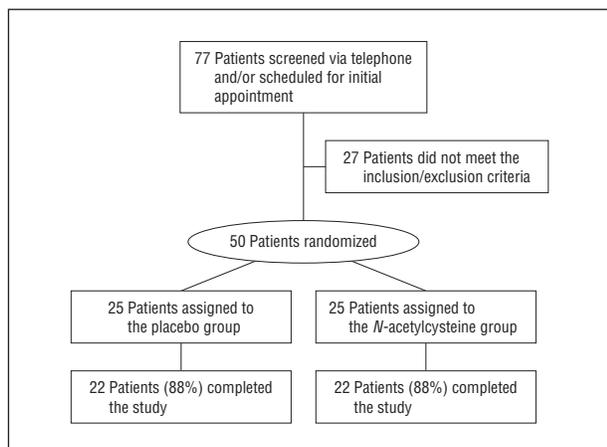

Figure 1. Patient flow diagram for *N*-acetylcysteine vs placebo in the treatment of trichotillomania.
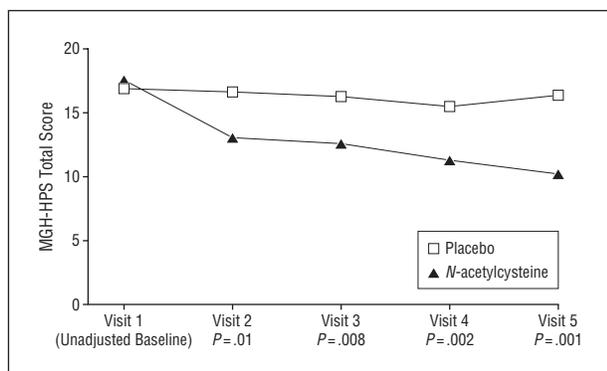
Figure 2. Massachusetts General Hospital Hair Pulling Scale (MGH-HPS) total scores adjusted for a baseline score of 17.18.

N-acetylcysteine group demonstrated significant improvement on the severity subscale ($F_{1,47}$=18.245) and on the resistance and control subscale ($F_{1,47}$=37.067;
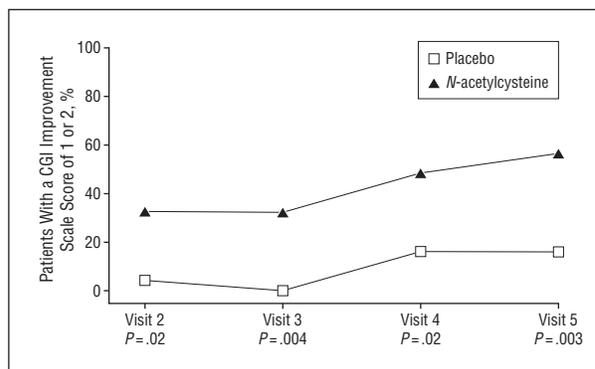
Figure 3. Percentage of patients with trichotillomania with a score of 1 or 2 on the Clinical Global Impression (CGI) improvement scale.

P<.001 for both) (Table 2). The PITS scores were consistent with the MGH-HPS total scores, and the difference between groups on the PITS was significant at the study end point ($F_{1,47}$=12.03; P=.001) (Table 2).

The CGI improvement scale score also demonstrated significant improvement by the study end point. Of patients assigned to the *N*-acetylcysteine group, 56% were "much" or "very much" improved by the study end point compared with 16% of those taking placebo (χ^{2}_{1}=8.681; P=.003) (**Figure 3**). Of patients assigned to receive *N*-acetylcysteine, 44% (n=11) had a 50% or greater reduction on the MGH-HPS compared with 0% in the placebo group (χ^{2}_{1}=14.103; P<.001). Of those who were "much" or very much" improved at the end point according to CGI scale score, a significantly larger percentage reported a 50% reduction in the MGH-HPS score compared with those who were not responders according to CGI scale scores (χ^{2}_{1}=12.850; P<.001).

Patients assigned to receive *N*-acetylcysteine, however, did not demonstrate greater response with respect to psychosocial functioning. Although functioning and

quality of life improved to a greater numerical extent for those assigned to the *N*-acetylcysteine group, neither the SDS total score ($F_{1,47}=2.683$; $P=.11$) nor the Quality of Life Inventory score ($F_{1,47}=1.337$; $P=.25$) demonstrated a significant difference between the 2 groups (Table 2).

Clinically significant change was calculated for the CGI severity scale. Patients with a CGI severity scale posttreatment score lower than 3 and a change from baseline of at least 2 points achieved a clinically significant change. Clinically significant change was seen in 11 (44%) patients assigned to the *N*-acetylcysteine group and in 1 (4%) of those assigned to the placebo group (Pearson $\chi_1^2=10.965$; $P=.001$).

Analyses performed on the subset of 44 patients who completed the study demonstrated significant reductions on all measures consistent with the intention-to-treat analyses.

Analysis of baseline variables demonstrated no significant moderators of treatment effect. Preexisting medication status, age, sex, age at trichotillomania onset, education, psychiatric comorbidity, previous treatment history, baseline trichotillomania severity, and psychosocial functioning measures were not statistically significantly correlated with treatment response. In addition, there were no differences in treatment response between patients who met the full *DSM-IV* diagnostic criteria for trichotillomania compared with those who did not.

SAFETY AND TOLERABILITY

There were no reported adverse experiences in patients who received *N*-acetylcysteine (**Table 3**). The few adverse experiences were of mild intensity and were reported only by those taking placebo. There were no statistically significant differences in the incidence of adverse events between groups. Mean HAM-D and HAM-A scores remained low throughout the study in both treatment groups (Table 2). No patient reported any subtle physiologic or mood changes that would have allowed him or her to suspect the condition to which they were assigned.

COMMENT

This randomized, double-blind, clinical trial indicates that *N*-acetylcysteine is safe and more effective than placebo for the treatment of trichotillomania. *N*-acetylcysteine was effective for trichotillomania on the primary and secondary outcome measures as assessed by physician and patient ratings, with medium to large effect sizes. The beneficial effects of *N*-acetylcysteine use were seen within 9 weeks of treatment initiation, and this result is consistent with those of previous studies that have found *N*-acetylcysteine therapy to be effective within days (3 days for the reduction of cocaine urges)[47] to a few weeks (8 weeks for gambling behavior).[29] *N*-acetylcysteine is an amino acid, is available in health-food stores, is cheaper than most insurance copayments, and seems to be well tolerated. *N*-acetylcysteine could be an effective treatment option for people with trichotillomania.

Table 3. Patients With Trichotillomania Reporting Any Adverse Drug Experiences

Adverse Drug Event	Patients, No. (%)		*P* Value[a]
	Placebo Group (n=25)	*N*-Acetylcysteine Group (n=25)	
Nausea	1 (4)	0	>.99
Diarrhea	2 (8)	0	.49
Cough	1 (4)	0	>.99

[a] Fisher exact test.

Patients assigned to receive *N*-acetylcysteine experienced a mean reduction (improvement) of 40.9% on the primary outcome measure (ie, MGH-HPS), and a responder rate of 56% (ie, "much" or "very much" improved on the CGI by the study end point). Although a variety of outcome measures have been used in previous studies, when we compare the present results with those of previous studies we find that the percentage reduction in the MGH-HPS score in this study is higher than that seen with medications (8.4%),[48] is similar to that reported for combined treatment (medications plus cognitive behavior therapy: 41.5%),[46] and is within the range of improvement reported for cognitive behavior therapy alone (34.8%-66.4% reduction in the MGH-HPS score).[49,50,57] These findings suggest that *N*-acetylcysteine compares favorably with existing treatment options available to physicians.

The efficacy of *N*-acetylcysteine in this study lends further support to the hypothesis that pharmacologic manipulation of the glutamate system (in the nucleus accumbens) may target core symptoms of compulsive behaviors. Pharmacotherapies that target the prefrontal glutamatergic drive to the nucleus accumbens,[25] such as *N*-acetylcysteine, may, therefore, correct the underlying pathophysiologic abnormalities and symptoms of trichotillomania. In addition, *N*-acetylcysteine increases cysteine and glutathione levels in glial cells.[51] Through its effects on glial functioning, *N*-acetylcysteine may be protective to glial cell functioning during hyperglutamatergic states and may enhance the glial uptake of glutamate by excitatory amino acid transporters.[52] Because glial cells are primarily responsible for the clearance of glutamate from the synapse,[53] this may be important for understanding the glutamate-modulating effects of *N*-acetylcysteine.

Although *N*-acetylcysteine may be a promising treatment for trichotillomania, previous pharmacologic studies[9] in trichotillomania have shown that particular treatments have not been effective for all individuals with trichotillomania. In the present study, 44% of patients treated with *N*-acetylcysteine did not respond. These results may reflect a failure to recognize the heterogeneity of individuals with trichotillomania and how that heterogeneity may necessitate individually tailored treatment approaches.[15] Recent research[54] has suggested that the obsessive-compulsive spectrum disorders may have various clusters that cohere based on clinical and possibly genetic grounds. Other trichotillomania research[55] has suggested that automatic compared with focused pull-

ing, and the degree of each type of pulling, may reflect meaningful differences in terms of clinical presentation, comorbid psychiatric disorders, neuropathophysiologic abnormalities, and treatment response. Although not examined in this study, differences in hair-pulling styles may also help identify subtypes of trichotillomania that respond differentially to *N*-acetylcysteine. Further research that examines various abnormalities of the impulsive-compulsive neurocircuitry may, therefore, result in the definition of a subtype of trichotillomania that is more likely to respond to glutamatergic agents, such as *N*-acetylcysteine, and a different trichotillomania subtype that may respond preferentially to serotonergic agents.[15] Although these notions remain speculative and require additional research to examine their appropriateness, one future direction for the treatment of trichotillomania may be to better define subtypes of trichotillomania (using clinical symptoms, cognitive testing, neuroimaging, and pharmacogenetics) to guide pharmacologic treatment selection.

Although there were numerically greater improvements in the functional and quality-of-life measures in this study for *N*-acetylcysteine compared with placebo, we did not find statistically significant improvement for patients taking *N*-acetylcysteine. The only previous trichotillomania study[46] that examined this question also found that neither cognitive behavior therapy nor medication use resulted in improved quality of life during an acute 12-week treatment trial. One possible explanation for the present findings might be the baseline scores. The patients in this study began with only mild functional impairment and a low-average quality of life. Given the limited range for improvement in these scales, it may not have been possible to see statistically significant improvement with the present sample size. Another explanation could be that the functional impairment and quality of life seen in patients with trichotillomania have more to do with the consequences of the pulling (eg, bald spots) than with the pulling itself. Because symptom improvement may occur many weeks before hair grows back, functional impairment and quality of life might be more relevant if measured after several months of symptom improvement. Finally, given that the Cohen *d* point estimate for the SDS was approaching a medium effect size, the nonsignificant findings for change in functional impairment might be due to low power for this measure (a bootstrap power analysis for the SDS resulted in an estimated power of 35.6% for $P < .05$).

This study represents, to our knowledge, the first trial of a glutamatergic agent in trichotillomania, but there exist several limitations. First, trichotillomania seems to be a chronic disease that may require long-term therapy. By design, this study did not assess treatment effects beyond the 12-week treatment period, and the longer-term effects of *N*-acetylcysteine therapy require further evaluation. It is possible that a longer course of therapy could result in continued and even greater reductions in trichotillomania symptoms. Second, this study did not include behavioral therapy. Cognitive behavior therapy has shown benefit for trichotillomania[9,56,57] and should be considered in con-

junction with pharmacotherapies. Finally, we have not yet examined the optimal *N*-acetylcysteine dose, and whether some patients would have responded to higher doses needs to be examined.

This investigation suggests that *N*-acetylcysteine may be effective in the acute treatment of trichotillomania. As effective treatments for hair pulling emerge, it becomes increasingly important that physicians and mental health care providers screen for trichotillomania to provide timely treatment.

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